Health Information and Quality Authority

An tÚdarás Um Fhaisnéis agus Cáilíocht Sláinte

Health Technology Assessment of the addition of severe combined immunodeficiency (SCID) to the National Newborn Bloodspot Screening Programme

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About the Health Information and Quality Authority (HIQA)

The Health Information and Quality Authority (HIQA) is an independent statutory authority established to promote safety and quality in the provision of health and social care services for the benefit of the health and welfare of the public.
HIQA's mandate to date extends across a wide range of public, private and voluntary sector services. Reporting to the Minister for Health and engaging with the Minister for Children, Equality, Disability, Integration and Youth, HIQA has responsibility for the following:

- **Setting standards for health and social care services** — Developing person-centred standards and guidance, based on evidence and international best practice, for health and social care services in Ireland.

- **Regulating social care services** — The Chief Inspector within HIQA is responsible for registering and inspecting residential services for older people and people with a disability, and children's special care units.

- **Regulating health services —** Regulating medical exposure to ionising radiation.

- **Monitoring services** — Monitoring the safety and quality of health services and children's social services, and investigating as necessary serious concerns about the health and welfare of people who use these services.

- **Health technology assessment** — Evaluating the clinical and cost-effectiveness of health programmes, policies, medicines, medical equipment, diagnostic and surgical techniques, health promotion and protection activities, and providing advice to enable the best use of resources and the best outcomes for people who use our health service.

- **Health information** — Advising on the efficient and secure collection and sharing of health information, setting standards, evaluating information resources and publishing information on the delivery and performance of Ireland's health and social care services.

- **National Care Experience Programme** — Carrying out national service-user experience surveys across a range of health services, in conjunction with the Department of Health and the HSE.

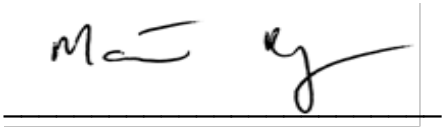
Foreword

The National Screening Advisory Committee (NSAC) was established in 2019 by the Minister for Health as an independent advisory committee to play a strategic role in the development and consideration of population-based screening programmes in Ireland. The role of the NSAC is to provide advice to the Minister for Health and the Department of Health on new screening proposals and proposed changes to existing screening programmes. At the request of the Department of Health, the Health Technology Assessment (HTA) directorate within the Health Information and Quality Authority (HIQA) undertakes evidence synthesis and provides evidence-based advice to NSAC on behalf of the Minister for Health.

Severe combined immunodeficiency (SCID) is an inherited inborn error of immunity affecting cell-mediated and humoral immunity, and constitutes one of the most severe forms of primary immunodeficiency. Typically presenting asymptomatically at birth, SCID is considered a paediatric emergency that is almost uniformly fatal in the first year of life without appropriate treatment. There are also implications for the childhood immunisation schedule whereby children with SCID should not receive live vaccines.

In the absence of screening, recognition and subsequent diagnosis of SCID relies on risk-based detection at birth or symptomatic presentation. Newborn screening for SCID is possible through the quantification of T-cell receptor excision circles (TRECs); however, it is not currently part of the National Newborn Bloodspot Screening Programme (NNBSP). The aim of screening is to enable earlier identification of those previously diagnosed on the basis of symptomatic presentation, thereby facilitating earlier disease management and treatment.

Work on the HTA was undertaken by an Evaluation Team from the HTA Directorate in HIQA. A multidisciplinary Expert Advisory Group was convened to advise the Evaluation Team during the course of the HTA. HIQA would like to thank the Evaluation Team, the members of the Expert Advisory Group and all who contributed to the preparation of this report.



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HIQA further notes that the findings set out in the advice represent the interpretation by HIQA of the available evidence and do not necessarily reflect the opinion of all members of the EAG.

The membership of the EAG was as follows:

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Conflicts of interest

None declared.

Key Findings and Advice to the National Screening Advisory Committee

In September 2021, the National Screening Advisory Committee (NSAC) requested the Health Information and Quality Authority (HIQA) to undertake a health technology assessment (HTA) of the addition of T-cell receptor excision circle (TREC)-based screening for severe combined immunodeficiency (SCID) to the National Newborn Bloodspot Screening Programme (NNBSP) in Ireland.

The key findings of this HTA, which informed HIQA's advice to NSAC, were:

- SCID is an inherited inborn error of immunity resulting from mutations in at least 19 known genes and impedes normal T-cell function. The condition is characterised by T-cell lymphopenia (TCL), that is, an absence or significantly depleted level of T-cells. Typically presenting asymptomatically at birth, SCID is considered a paediatric emergency, which is almost uniformly fatal in the first year of life without appropriate treatment.
    - International diagnostic and treatment guidelines exist for SCID, with Children's Health Ireland (CHI) at Crumlin acting as the national tertiary referral centre for children with suspected SCID. SCID can be treated successfully if diagnosed early; allogeneic haematopoietic stem cell transplant (HSCT) is the primary treatment and is potentially curative. These transplant procedures largely take place in Great North Children's Hospital in Newcastle upon Tyne, United Kingdom.
    - Children with SCID should not receive live vaccines (for example, rotavirus); however, given the timing of immunisation schedules, in the absence of screening or known family history, a child may receive such vaccines prior to being identified as having SCID.
- In Ireland, cases of SCID are currently identified by family history (typically a sibling previously diagnosed) or through clinical presentation (typically through the development of infections), and, since May 2022, through screening for ADA-SCID (one specific subtype of SCID that may be screened for using tandem mass spectrometry). As a result, currently, some diagnoses of SCID are delayed. Also, it is possible that some cases may be missed (that is, infants may die prior to diagnosis).
- The NNBSP is offered to all newborns in Ireland within the first 72 to 120 hours of life through the collection of a dried bloodspot sample which is tested at the National Newborn Bloodspot Screening Laboratory (NNBSL). The

current programme screens for nine conditions, with the most recent change being the addition of screening for ADA-SCID. This HTA considered the potential addition of TREC-based screening for all SCID subtypes to the existing NNBSP panel, which includes ADA-SCID screening using tandem mass spectrometry.

- Newborn screening for SCID is possible through the quantification of TRECs, which are a DNA by-product produced during normal T-cell development and hence act as a surrogate marker: an absence, or depletion, of TRECs is indicative of TCL. SCID represents just one cause of TCL. Where the primary target is SCID, the aim is to ensure the TREC cut-off defined during initial verification does not miss cases of SCID (that is, minimising false negatives) while remaining as specific as possible (that is, minimising false positives and the extent to which non-SCID TCLs are detected).
- Internationally, there has been a move towards newborn screening for SCID. Based on a review of 34 countries, as of September 2022, newborn screening for SCID has been implemented in seven European countries, New Zealand, and the United States. In a further nine countries, screening was subject to regional implementation, ongoing implementation, piloting or was under consideration. No clinical pathways or guidelines were identified from these international sources for the management of non-SCID TCLs detected during newborn screening.
- In Ireland, between 2005 and 2020, there were 27 cases of SCID diagnosed, indicating a birth prevalence of 1 in 39,760 births. Approximately half (n = 14) of the cases diagnosed were ADA-SCID, with the majority of these (n = 13) being from the Irish Traveller population. Of the 27 cases, eight infants were identified by risk-based detection at birth, and 19 were diagnosed clinically (for example, on the basis of symptoms of infection). Over the 15-year period, three infants with SCID types other than ADA-SCID were diagnosed at birth, and 10 were diagnosed clinically.
    - Screening for ADA-SCID was introduced in Ireland in May 2022. If screening for all types of SCID were also adopted, the added benefit would be limited to the detection of cases of SCID that are not already detected through screening for ADA-SCID.
- A systematic review of TREC-based newborn screening programmes for SCID was undertaken with the primary outcome of interest being test accuracy of TREC-based screening for SCID and for TCL generally (including SCID), as measured through rates of detection of these conditions. Twenty-seven

relevant articles were identified which described twenty-seven unique cohorts across 19 studies:

- There was notable heterogeneity in terms of the screening algorithms and TREC cut-off values used. The method of measuring TRECs (for example, the kit used), the TREC cut-off, the screening algorithm, and the diagnostic criteria in use by a screening programme are important. These influence the rate of overall referral for confirmatory testing and the extent to which non-SCID TCLs and instances of false positives are detected.

- The positive predictive value (PPV) for SCID (excluding other TCL causes) ranged from 0.80% to 20.00%; these figures describe, within all tests that had an abnormal screen result, the percentage that were SCID cases. The PPV for all TCL (including SCID) across studies ranged from 20.29% to 89.36%; these figures describe, within all tests that had an abnormal screen result, the percentage that were TCL cases (SCID and non-SCID TCLs).

- The false positivity rate across all studies was less than or equal to 0.09%; this figure represents those who had an abnormal screen result but who subsequently were found not to have either SCID or another TCL. Considering the highest rate reported, in the Irish context, this would equate to up to 52 false positive results per year, assuming an annual cohort size of approximately 58,000 infants.

- Of note, the incidence of non-SCID TCLs detected through a newborn bloodspot screening (NBS) programme would likely be higher than that of SCID.

    - Within the identified studies, the ratio of SCID to non-SCID TCLs detected ranged from 1:2 to 1:38. This range likely reflects the differing TREC cut-offs and algorithms used for an abnormal screen result in the individual screening programmes.

    - Five studies provided sufficient detail of the breakdown of the causes of non-SCID TCLs identified. On average across the studies, 50% of the non-SCID TCLs occurred as part of congenital syndromes (that is, a group of signs or symptoms that occur together and collectively characterise an abnormal condition), 24% were secondary to other causes (for example, maternal immunosuppression), and 26% were idiopathic. Given the distribution of these causes, and as TCL is associated with

the development of infections, it is plausible that a substantial proportion of non-SCID TCLs would present clinically (either due to syndromic signs and symptoms or on the basis of infection) in the absence of their detection through TREC-based screening for SCID.

- Abnormal TREC screening results occur due to SCID, non-SCID TCLs and due to false positives. Where an abnormal TREC screen result is obtained, further testing would be required.
    - In the case of SCID, international diagnostic and treatment guidelines would be followed.
    - Non-SCID TCLs are a clinically heterogeneous group with a diverse range of underlying causes; they comprise congenital and secondary causes of TCL (other than SCID), idiopathic TCL, and transient instances of TCL (such as TCL occurring in preterm infants). For non-SCD TCLs, follow-up would include outpatient attendance for confirmatory testing followed by initiation of clinical care appropriate to the condition detected.
    - Follow-up of false positive results would involve one outpatient appointment for confirmatory testing, including a blood draw and subsequent communication with parents to relay the false positive finding and to alleviate concerns.
- National and international data consistently suggest that the age at which children are diagnosed with SCID, and, consequently, the age at which they undergo definitive treatment, is lower for those identified on the basis of screening or family history compared with those diagnosed clinically. Similarly, there is evidence to suggest that the number of complications (including vaccine-derived health problems) and infections prior to diagnosis, prior to treatment, active at the time of treatment, and post-treatment, tends to be higher in those diagnosed clinically compared with those identified on the basis of screening or family history. Infants who do not have infections up to the time of definitive treatment have a better prognosis than those who have such infections.
- A systematic review was undertaken to examine the potential clinical benefits associated with early diagnosis and or HSCT, compared with late diagnosis and or HSCT. Primary outcomes of interest were safety and survival in those diagnosed with SCID, as associated with early diagnosis and or HSCT, and compared with late diagnosis and or HSCT. Fifteen publications, presenting

data on 13 unique cohorts, were included, with all studies presenting results for survival outcomes. No safety data were identified with respect to adverse events (for example, procedural-based events or complications) associated with early versus late HSCT for the treatment of SCID.

  - The majority of studies provided evidence to suggest that early diagnosis and or HSCT led to improved survival outcomes compared with late diagnosis and or HSCT.

  - The majority of evidence within this review related to survival. Limited additional data were found for the impact on neurological events (one study), and on growth percentiles (two studies). Findings for other clinical outcomes were not identified from this limited evidence base, though it is plausible that, among children with long-term survival following definitive treatment, early diagnosis (and consequently early HSCT) may also confer reductions in morbidity in the long-term.

  - The evidence base addressing this question is derived from observational studies that were primarily informed by retrospective review across several decades in multiple international settings. Additionally, the studies were typically not formally designed to establish causality for the relationship between early versus late diagnosis, and or HSCT. These limitations reflect challenges in research related to rare diseases generally. However, the findings identified represent the best available evidence at this time. The evidence consistently suggests that earlier diagnosis and or HSCT is associated with improved clinical outcomes and survival for children with SCID.

- A systematic review was undertaken to identify the available international evidence on the cost effectiveness of universal TREC-based newborn screening for SCID compared with either screening for ADA-SCID alone or no screening.

  - No study directly considered the cost effectiveness of SCID screening where screening for ADA-SCID was already in place.

  - Compared with no screening for SCID, the majority of studies suggested that universal TREC-based screening for SCID would be potentially cost effective, in the context of the typical willingness-to-pay (WTP) thresholds used in Ireland.

  - In understanding the potential relevance of the results of the review, it is important to note that, were screening for ADA-SCID in place, the

incremental benefits would be expected to be lower; this is because a proportion of the cases would already have been detected through such screening. However, the incremental costs would not be expected to be correspondingly lower. This would be expected to result in higher incremental cost-effectiveness ratios (ICERs) (that is, it would be less cost effective) than the estimates observed.

- Given limitations in existing data, it is unlikely that there would be sufficient data available to support a model specific to the Irish context. The cost effectiveness relative to a situation where ADA-SCID screening is in place (as is the case in Ireland) is unclear. Cost effectiveness depends in part on the number of cases that would be detected by TREC-based screening beyond those currently detected by ADA-SCID screening and detection based on family history. This is uncertain, in part due to the potential for a population of cases that are currently undiagnosed (that is, those who may die prior to clinical presentation).

- A budget impact analysis was undertaken to estimate the incremental budget impact associated with the addition of TREC-based screening for SCID to the current standard of care. The total incremental budget impact is estimated at €3.66 million over a five-year time horizon. This analysis was undertaken in two parts to reflect costs associated with different parts of the screening programme:

  - Verification and implementation of screening (for example, costs associated with laboratory equipment and staffing) was estimated to cost €3.0 million. The incremental budget impact was driven largely by the cost of the TREC test kit (consumables), equipment and labour. In one-way sensitivity analysis, the unit cost per TREC test kit was the major contributor of uncertainty to the incremental budget impact.

  - Diagnosis and treatment costs (for example, costs associated with hospital admission or outpatient appointments) for children with SCID and children with non-SCID TCLs were estimated at approximately €660,000 in total. In the base case it was assumed that those currently identified by clinical presentation would be detected earlier, and an additional case of SCID would be detected every two years, though this is very challenging to reliably estimate. The majority of this incremental budget impact was associated with the assumed identification of SCID cases that would not have been diagnosed in the absence of screening (that is, those who may die prior to clinical presentation). Given the very high uncertainty with this assumption, it was varied in scenario

analyses and identified as a key driver of this part of the budget impact analysis.

- The process of adding new conditions to the NNBSP is complex and requires a collaborative and programme-centred approach. Key organisational requirements and considerations relevant to the addition of TREC-based screening for SCID include the:
    - recruitment of additional laboratory staff to enable its verification and ongoing implementation
    - procurement of new equipment and training of laboratory personnel, given that this form of testing is not currently in place
    - verification of the testing method and the establishment of the screening algorithm, including consideration of elements such as inconclusive results, prematurity and those in intensive care, and the interpretation of results relative to other tests on the NNBSP
    - timing of implementation relative to the move of the NNBSL to the new children's hospital. Implementation at the current site in CHI Temple Street would be associated with:
        - a need for structural modification to accommodate additional space requirements (namely, two dedicated rooms)
        - competing demands for finite project management capacity in the context of the ongoing requirements to manage the impending move of the NNBSL
    - updating of parent and sample taker information, and referral pathways
    - required updates to the NNBSP quality assurance programme. In particular, if TREC-based screening for SCID is implemented, consideration should be given to monitoring and evaluating the continuing relevance of screening for ADA-SCID alongside TREC-based screening.
- Assay verification, which would be undertaken prior to implementation, aims to maximise the identification of SCID cases and to minimise the risk of false positives and the detection of non-SCID TCLs of potentially unknown clinical significance. Consistent with standard practice in the NNBSP, following implementation, provisional TREC cut-offs set during assay verification would be reviewed and revised as necessary when evaluating screening outcomes.

- The ethical and social considerations associated with the introduction of this form of screening include the:
    - benefit-harm balance, which differs between and within the multiple groups that may be detected. There is clear benefit for children with SCID in terms of improved clinical outcomes, variable potential for benefit in the case of non-SCID TCLs, and no benefit for those identified as false positives.
        - There is a requirement for information to be provided in a clear, consistent and timely manner in the context of an abnormal result. The method of communicating abnormal screening test results should therefore be considered in terms of its potential to impact on the parents and family of the newborn.
    - protection of autonomy when considering the provision of information and obtaining of informed consent, particularly in the context of the incidental findings that may be detected and that the programme would be using two different tests to screen for one condition (that is, ADA-SCID)
    - perspective of justice and equity when considering uncertainties in the clinical and economic impact of such an addition
    - timing of this assessment relative to the recent addition of ADA-SCID screening to the NNBSP and the ongoing assessment of HSCT repatriation.
- For conditions that meet the evidence bar for inclusion in the NNBSP, there may be efficiencies for the programme if implementation is deferred until a number of changes to the programme can be made at the one time rather than proceeding with sequential additions (that is, as soon as a positive recommendation is made). These efficiencies relate to the verification processes (particularly for conditions which may be screened for using the same technology), training requirements, and programme adjustments. However, efficiencies for the programme would need to be weighed against the individual clinical benefit for children identified through screening.

Arising from this HTA, HIQA's advice to NSAC is as follows:

- SCID is a rare, but serious inherited condition which is almost uniformly fatal in the first year of life without appropriate treatment. Compared with international data, the estimated prevalence of diagnosed SCID in Ireland is

relatively high at 1 in 39,760 births, with 27 patients diagnosed from 2005 to 2020.

- National and international evidence consistently suggests that earlier identification, and earlier treatment, for SCID results in better clinical outcomes for the child in terms of reduced morbidity and mortality. Children with SCID should not receive live vaccines. Early identification of infants with SCID through screening is important in order to avoid harms and to maintain confidence and trust in the national immunisation programme.
- Screening for ADA-SCID (which accounts for approximately half of SCID cases in Ireland) was implemented as part of the NNBSP in May 2022. SCID is also currently identified through risk-based detection at birth (for infants with a family history) or, later, through clinical presentation.
- The addition of TREC-based screening for SCID would enable the earlier detection of infants that will otherwise present clinically. Such screening could also detect infants that would otherwise experience early mortality prior to diagnosis.
- While considered sensitive, TREC-based screening is not specific to SCID. Other T-cell lymphopenias (TCLs) would also be identified, and it is likely that the incidence of these non-SCID TCLs detected through screening would be higher than that of SCID.
- The incremental budget impact of adding TREC-based screening was estimated at €3.66 million over five years. This estimate was driven largely by the cost of the TREC test kit, new equipment, laboratory staff, and the potential for an increase in post-screening prevalence.
- There are a number of key operational challenges and considerations relevant to any decision to implement screening. These include:
    - the need to establish and verify the testing method and screening algorithm in terms of the defined screening target and the population in Ireland
    - the timing of implementation, given the scheduled move of the NNBSL to the new children's hospital.
- From an ethical and social perspective, the benefits of screening for children with SCID, their families and the broader health system should be weighed against the potential for harm in the context of instances of false positives and

the non-SCID TCLs detected through screening (not all of which would be clinically relevant or will benefit from earlier detection).

- The NNBSP has an established quality assurance programme. If TREC-based screening for SCID is implemented, consideration should be given to monitoring and evaluating the continuing relevance of screening for ADA-SCID alongside TREC-based screening.

Executive Summary

A health technology assessment (HTA) is a multidisciplinary process that summarises information about the medical, social, economic, and ethical issues related to the use of a health technology and does so in a systematic, transparent, unbiased, and robust manner. A HTA is intended to support evidence-based decision-making regarding the optimal use of resources in healthcare services.

This report summarises the findings of a HTA on the potential addition of screening for severe combined immunodeficiency (SCID) using T-cell receptor excision circles (TRECs) to the National Newborn Bloodspot Screening Programme (NNBSP).

Background

SCID is an inherited inborn error of immunity affecting both cell-mediated and humoral immunity, and constitutes one of the most severe forms of primary immunodeficiency. Typically presenting asymptomatically at birth, SCID is considered a paediatric emergency that is almost uniformly fatal in the first year of life without appropriate treatment. The main treatment for SCID is haematopoietic stem cell transplant (HSCT), which serves to establish a functioning immune system in the child. Screening for one specific form of SCID, ADA-SCID, was implemented by the NNBSP in Ireland in May 2022; this form of SCID may be detected using a screening platform already in place within the NNBSP (tandem mass spectrometry).

In September 2021, at the request of the National Screening Advisory Committee (NSAC), the Health Information and Quality Authority (HIQA) agreed to undertake a HTA on the potential addition of TREC-based screening for SCID to the NNBSP. TREC-based screening for SCID is intended to detect all SCID subtypes, including ADA-SCID. The HTA considered the potential addition of TREC-based screening for all SCID subtypes to the existing NNBSP panel, which includes ADA-SCID screening using tandem mass spectrometry.

Methods

This research was carried out in accordance with HIQA's guidelines for the conduct of HTAs. In summary, the following took place:

- The Terms of Reference of the HTA were agreed between HIQA and the Department of Health.
- An Expert Advisory Group (EAG) was convened by HIQA comprising representation from relevant stakeholders. These included the Department of Health, the Health Service Executive (HSE), the National Immunisation

Advisory Committee, the NNBSP, National Newborn Bloodspot Screening Laboratory (NNBSL), clinicians with specialist expertise in paediatric immunology, public health, haematology, clinical genetics, patient and public representatives (Irish Primary Immunodeficiencies Association, 22q11 Ireland, and Cuidiú), methodological and international experts. An Evaluation Team was appointed comprising HIQA staff.

- The current NNBSP, diagnostic and treatment pathways for SCID, and the mechanism, and international use, of TREC-based screening for SCID were described.
- The epidemiology of SCID in Ireland and internationally was described.
- A systematic review of TREC-based newborn screening for SCID was performed.
- A systematic review of early versus late diagnosis and or HSCT for the treatment of SCID was performed.
- A systematic review of the cost effectiveness of newborn screening for SCID was performed.
- The resource and budget implications of introducing newborn screening for SCID in Ireland were estimated.
- Wider organisational, ethical, and societal implications that newborn screening for SCID may have for children, families, the general public, and the healthcare system in Ireland were described.
- A draft report summarising the findings of this HTA was produced and circulated to the EAG for review and subsequently amended, where appropriate.
- Following a meeting of the EAG, the final draft of the report for the HTA was amended and HIQA's advice to NSAC circulated to the EAG for consideration.
- Following review by the EAG, the final draft of the HTA was submitted to the Board of HIQA for approval.
- Following its approval, the finalised HTA was submitted to NSAC for consideration and published on the HIQA website.

Description of technology

SCID is typically characterised by T-cell lymphopenia (TCL) (that is, a significantly depleted level of functioning T-cells), with varying impact on other immune markers such as B-cells and natural killer cells. In the absence of early, risk-based detection or screening, SCID presents clinically at approximately three to six months. The infant typically presents with recurrent and often severe infections, and non-infectious complications such as a failure to thrive.

In addition to symptoms resulting from infections, there are important implications of SCID for early childhood immunisation programmes; children with SCID should not receive live viral or bacterial vaccines (for example, rotavirus), given the potential for severe illness and mortality due to the inability of children with SCID to mount an appropriate immune response. However, given the timing of immunisation schedules, in the absence of screening or a known family history, a child with SCID may receive such vaccines prior to being recognised as having immunodeficiency, which may result in harm to the child.

In Ireland, cases of SCID are currently identified by family history (typically a sibling previously diagnosed) or through clinical presentation (typically through the development of infections), and, since May 2022, through screening for ADA-SCID (one specific subtype of SCID that may be screened for using tandem mass spectrometry). As a result, currently, some diagnoses of SCID are delayed. Also, it is possible that some cases may be missed (that is, infants may die prior to diagnosis).

If SCID is suspected based on family history, clinical presentation or the results of screening, the child is referred to the Department of Paediatric Infectious Diseases and Immunology, Children's Health Ireland (CHI) at Crumlin, Dublin. The diagnosis of SCID is established using a range of tests, as appropriate; these may include routine blood tests, flow cytometry, T-cell proliferation analysis, maternal engraftment analysis, and molecular testing for specific mutations.

Screening is used to identify individuals from an apparently healthy, asymptomatic, population who are at higher risk of a particular condition. The overall aim of screening is to provide an early treatment or intervention and, hence, better outcomes than if individuals present symptomatically or later in the disease course.

This assessment considers the addition of TREC-based testing for SCID to the NNBSP in Ireland. The NNBSP is offered to all newborns in Ireland within the first 72 to 120 hours of life. Screening is performed through the collection of dried bloodspot samples (the 'heel-prick test'), with samples tested at the NNBSL. The current programme screens for nine conditions with the recent addition of ADA-SCID screening by tandem mass spectrometry.

Newborn screening for SCID, using dried blood spot samples, is possible through the quantification of TRECs, which are a by-product of normal T-cell development and hence act as a surrogate marker for the number of T-cells in an infant's blood. An absence or depletion of TRECs is indicative of TCL. The TREC test is performed using DNA extracted from a sample of a collected dried bloodspot sample. Appropriate cut-off values and algorithms are established and validated at the local level. While the primary target of TREC-based screening may be SCID, other patient groups may receive an abnormal TREC screen, including those with non-SCID TCLs and instances of false positive results. Where an abnormal TREC screen result is obtained, further testing would be required.

In terms of current international practice regarding newborn screening for SCID, a review of 34 countries was conducted including those in the European Economic Area, United States, Canada, Australia and New Zealand. Newborn screening for SCID was fully implemented in nine countries, regionally implemented in three countries, under implementation in one country, under review and or being piloted in four countries, and, in one country, had received a positive recommendation for implementation following a HTA and pilot. No clinical pathways or guidelines were identified for the management of non-SCID TCLs from these international sources.

Once the diagnosis of SCID has been established, HSCT from a matched sibling donor, or other matched family donors, is considered the gold standard treatment and is potentially curative. HSCT is a process by which haematopoietic stem cells from a donor are transplanted to the patient by infusion. The transplanted cells then ideally develop into functional T-cells with the overall aim of HSCT being immune reconstitution (that is, the rebuilding of the immune system to be able to protect against infection). While successful HSCT may resolve the immune deficiency associated with SCID, other symptoms of SCID and whose occurrence depend on the SCID subtype may not be resolved (for example, non-immunological sequelae arising from the genetic defect). Currently for Irish cases, with a limited number of exceptions, HSCT and immediate aftercare is completed in the United Kingdom with patients transferred back to CHI at Crumlin, Dublin, for long-term follow-up. At the time of writing, HIQA is undertaking a separate HTA to inform a decision by the HSE regarding the repatriation of HSCT services for such patients to Ireland.

Epidemiology

SCID results from mutations in at least 19 known genes, and thus a large number of subtypes exist. Substantial clinical heterogeneity exists within SCID; this is the case within groups of patients with mutations in the same gene, and even between individuals with near identical gene mutations. Amorphic mutations (that is, a loss of gene function) result in typical SCID whereas hypomorphic mutations (that is, when

a gene product exhibits reduced rather than absent activity) in several of the genes that cause SCID may result in Omenn syndrome or atypical SCID (also known as "leaky" SCID).

The genetic pattern of inheritance for the majority of the mutations causing SCID is autosomal recessive (that is, passed down from both parents). The typical exceptions are IL2RG mutations, whose inheritance is X-linked recessive, and RAC2 mutations, which are autosomal dominant (that is, passed down from one parent). As a result of the genetic patterns of inheritance associated with SCID, overall risk factors include family history and consanguinity (that is, unions between individuals who are related).

Given the diversity of genetic mutations associated with SCID, the incidence is noted to vary widely across geographic locations and within populations. In the absence of newborn screening, the incidence of SCID is considered to be underestimated, that is, there may be a level of infant mortality prior to diagnosis. Within Ireland, between 2005 and 2020, there were 27 children diagnosed with SCID. Over this 15 year time period, there were 1,073,519 births registered, reflecting an overall birth prevalence of 1 in 39,760 births. Collectively, Ireland presents with a higher proportion of ADA-SCID relative to other international locations with 14 (51.8%) of the 27 identified SCID cases being of the ADA-SCID subtype specifically. Thirteen (92.9%) of these ADA-SCID cases were of Irish Traveller ethnicity (with a previously documented founder mutation in this population). The recently implemented ADA-SCID screening will now detect ADA-SCID cases. If screening for all types of SCID were also adopted, the added benefit would be limited to the detection of cases of SCID that are not already detected through screening for ADA-SCID. Of the 27 SCID cases reported in Ireland between 2005 and 2020, eight infants were diagnosed through risk-based detection at birth while 19 were diagnosed clinically. Excluding cases of ADA-SCID (as these will now be detected through screening), three infants with subtypes other than ADA-SCID were diagnosed at birth and 10 were diagnosed clinically.

Clinical presentation of SCID typically manifests as recurrent and often severe infections, non-infectious health conditions (for example, failure to thrive), and vaccine-derived health problems. There is evidence internationally that detecting SCID by clinical presentation alone results in a later age at diagnosis. In Ireland, the median age for those diagnosed through risk-based detection at birth was 0 days (range 0 to 14) compared with a median of 98 days (range 20 to 229) for those diagnosed clinically.

Infections in children with SCID can include common bacterial and viral infections as well as opportunistic fungal infections. Typically, these infections result in lower

respiratory tract infections, upper respiratory tract infections, or gastrointestinal infections. Across the 27 SCID cases in Ireland, 47 documented infections were noted prior to treatment, with three occurring in the group of eight infants diagnosed at birth and 44 in the group of 19 infants diagnosed clinically, illustrating clear instances of multiple infections for a number of infants. Nine infections secondary to live vaccination were documented across the 27 SCID cases. All of these occurred in those who were diagnosed clinically. At the national and international level, there is evidence to suggest that the number of infections prior to diagnosis, prior to treatment, and active at the time of treatment tends to be higher in those diagnosed clinically compared with those identified on the basis of screening or family history.

In addition to severe infections, individuals with SCID may also experience non-infectious complications. These complications may include growth delays or insufficient weight gain, termed 'failure to thrive', and organ damage, which may result in pulmonary, neurologic or gastrointestinal conditions. Failure to thrive was the most common complication other than infection documented in the Irish cohort with 14 such instances; all of these cases occurred in those who were diagnosed clinically as opposed to at birth.

From the 27 cases of SCID in Ireland diagnosed between 2005 and 2020, 25 (92.6%) survived to definitive treatment, while two cases of mortality occurred prior to treatment; both of these cases occurred in the group diagnosed clinically. The median age at definitive treatment was 54 days (range 24 to 258) for those identified through risk-based detection at birth and 184 days (range 67 to 354) for those diagnosed clinically. Twenty-four children were alive at 24 months follow-up while one child, who had been diagnosed clinically, died shortly after transplant. Thus, three out of 19 of those diagnosed clinically had died, whereas all eight diagnosed at birth were still alive at follow-up.

Systematic review of TREC-based newborn screening for SCID

A systematic review of TREC-based newborn screening for SCID was undertaken. The primary outcome of interest was the test accuracy of TREC-based screening for SCID and for TCL generally (SCID and non-SCID TCL), as measured through rates of detection of these conditions. Secondary outcomes included rates of retest (that is, repeat TREC analysis being performed on the same dried bloodspot (DBS)), repeat DBS requests (that is, a new sample being taken from the infant), and rates of referral (that is, for confirmatory testing), alongside any additional measures of effectiveness reported, such as programme uptake rates and perceptions of the programme.

Twenty-seven relevant articles were identified, which included 27 unique cohorts presented by 19 studies. Fifteen studies reported the outcomes of TREC-based screening in isolation, three reported outcomes of combined TREC and kappa-deleting recombination excision circles (KREC)-based screening (that is, an additional test for B-cell lymphopenia), and one reported TREC in combination with an embedded next-generation sequencing panel. To note, for the latter two study types, TREC results could not be isolated for reporting, and therefore only the results from the first type of study are described here. There was notable heterogeneity in terms of the screening algorithms, test methodologies, and TREC cut-off values used. A number of studies further reported changes over the course of the study period to the TREC cut-off used for the included cohorts.

Rates of retest (range 0.24% to 2.03%), repeat DBS requests (range 0.02% to 0.61%), and onward referrals (range 0.02% to 0.11%) varied across the included cohorts, but were generally low as a proportion of the total population screened. The positive predictive value (PPV) for SCID ranged from 0.80% to 20.00% with no clear trend in terms of the different TREC cut-off values used; these figures describe, within all tests that had an abnormal screen result, the percentage that were SCID cases. The PPV for all TCL (including SCID and non-SCID TCL) ranged from 20.29% to 89.36%; these figures describe, within all tests that had an abnormal screen result, the percentage that were TCL cases (SCID and non-SCID TCLs). Of note, this range excludes one outlying PPV of 100%, which would be a highly unusual result in the context of population based screening; seven studies reported a PPV of 70% or higher. Some consistency was noted in terms of lower TREC cut-offs generally having higher PPVs. In terms of PPV, it should be noted that cut-offs used will depend on test methodologies and algorithms in place so direct comparisons across studies are limited in value.

As a percentage of the total population screened, the false positivity rate (following exclusion of TCLs) was less than or equal to 0.09% across the included cohorts. Considering the highest rate reported, in the Irish context, this would equate to up to 52 false positive results per year, assuming an annual cohort size of approximately 58,000 infants. A wide range of potential causes of non-SCID TCL were reported, including congenital syndromes (such as 22q11.2 Deletion Syndrome), secondary causes (such as maternal immunosuppression), and those which are idiopathic in nature (which may be transient or persistent). The detection level of such non-SCID TCLs will vary depending on the TREC cut-off, screening algorithm, and diagnostic criteria in use. However, it is important to consider that the incidence of non-SCID TCLs detected through newborn bloodspot screening (NBS) programmes would likely be higher than that of SCID. Within the identified studies, the ratio of SCID to non-SCID TCLs detected ranged from 1:2 to 1:38. This

range likely reflects the differing TREC cut-offs and algorithms used for an abnormal screen result in the individual screening programmes. Five studies further provided sufficient detail of the proportional breakdown of the causes of non-SCID TCLs identified. On average across the studies, 50% of the non-SCID TCLs occurred as part of congenital syndromes (that is, a group of signs or symptoms that occur together and collectively characterise an abnormal condition), 24% were secondary to other causes (for example, maternal immunosuppression), and 26% were idiopathic. Given the distribution of these causes, and as TCL is associated with the development of infections, it is plausible that a substantial proportion of non-SCID TCLs would present clinically (either due to syndromic signs and symptoms or on the basis of infection) in the absence of their detection through TREC-based screening for SCID.

A limited number of missed cases were reported across the included studies with three cases of delayed-onset leaky SCID and one case of combined immunodeficiency noted as having been missed. Given that the included studies typically did not follow participants up systematically, this likely represents an underestimate of missed cases for TCL generally. However, in the context of the severity of SCID, should a case be missed, it is probable that they would present clinically in the first year of life.

The uptake rate of newborn screening for SCID was presented for two population-based cohorts and three pilot cohorts, with a notably high uptake (≥98%) reported for all but one pilot study, which was undertaken within the Navajo Nation in the United States (61%). One pilot study conducted in the Netherlands investigated parent perceptions of newborn screening for SCID through surveys and interviews. The authors noted that support for newborn screening for SCID was expressed by the majority of parents. Of parents interviewed who had a child with an abnormal result, the authors noted themes of anxiety and stress when receiving an abnormal screening result, alongside the importance of good communication in the informing of such results.

Systematic review of early versus late diagnosis and or HSCT

A systematic review was undertaken to examine the potential clinical benefits associated with early diagnosis and or HSCT compared with late diagnosis and or HSCT. Primary outcomes of interest were safety and survival.

Fifteen publications, presenting data on 13 unique cohorts, were included in the systematic review. Apart from one prospective cohort study, all were retrospective cohort studies. Only two studies stratified participants into two independent groups and specifically compared the groups based on whether or not the infant received an

early SCID diagnosis and or access to HSCT. The remaining studies considered the potential effect of early diagnosis and or treatment within single cohorts, as part of a broader analysis of a wide range of factors that could have impacted clinical outcomes.

There was noted heterogeneity in terms of the descriptions of 'early' versus 'late' diagnosis and or HSCT. Four studies considered early versus late diagnosis, two of which examined the impact of early diagnosis, with 'early' described as diagnosis antenatally or at birth, and 'late' described as diagnosis after birth. The remaining two studies compared those identified on the basis of family history or NBS versus those diagnosed clinically, as well as comparing outcomes for patients who received HSCT before or after 3.5 months of life. Eleven studies compared age at receipt of HSCT based on different age cut-off definitions, which included before or after 28 days of life, four months of life, 3.5 months of life, and six months of life. A cut-off definition of 3.5 months was most frequently used (n = 6).

All included studies reported results for survival outcomes. No safety data associated with adverse events (for example, procedural based events or complications) relating specifically to early versus late HSCT for the treatment of SCID were identified. Overall, 12 of the 13 independent studies provided evidence to suggest that early diagnosis and or HSCT was associated with improved survival outcomes compared with late diagnosis and or HSCT. Three out of four studies, which considered early versus late diagnosis, showed improved outcomes in favour of earlier diagnosis. The fourth study did not observe a significant difference in outcomes in terms of early versus late diagnosis. However, this study also investigated the effect of age at HSCT and observed a significant effect for this comparison. Ten out of 11 studies which included a comparison based on age at HSCT indicated higher survival in those receiving HSCT at an earlier age. The majority of evidence within this review related to survival; limited evidence was identified for outcomes relating to neurological events and growth percentiles making it challenging to draw firm conclusions. Findings for other clinical outcomes were not identified from this limited evidence base, though it is plausible that, among children with long-term survival following definitive treatment, early diagnosis (and consequently early HSCT) may also confer reductions in morbidity in the long-term.

Eight studies reported the effect of pre-HSCT infections on survival outcomes; all observed that the presence of infections prior to HSCT negatively impacted overall survival. Further scrutiny of study findings suggested that differences in outcomes reported for early versus late HSCT may be a proxy for infection status prior to and up to the point of HSCT. Improved outcomes in infants diagnosed with SCID or in

receipt of HSCT at a relatively earlier age might be explained by lower risk of complications due to infection.

The evidence base addressing this question is derived from observational studies that were primarily informed by retrospective review across multiple international settings, and across several decades. Furthermore, the studies identified by this review were not formally designed to establish causality for the relationship between early versus late diagnosis, and or HSCT, and outcomes such as survival. These limitations reflect challenges in research related to rare diseases generally. However, the findings identified represent the best available evidence at this time. The evidence consistently suggests that earlier diagnosis and or HSCT is associated with improved clinical outcomes and survival for children with SCID.

While the focus of this chapter was the direct benefits accruing to the child screened in terms of clinical outcomes, it is acknowledged that there may be additional benefits to the child, parent and family members in terms of early diagnosis and treatment, including reducing the extent of the diagnostic odyssey and, thereby, potential associated reduction of anxiety and stress.

Systematic review of the cost effectiveness of newborn screening for SCID

A systematic review was undertaken to identify the available international evidence on the cost effectiveness of universal newborn screening for SCID, by TREC quantification, compared with either no screening or with screening for ADA-SCID alone. No study was identified that compared universal screening for SCID with screening for ADA-SCID alone; 11 independent studies were identified that compared with no screening. Ten of the studies were model-based, and one was based on empirical data from a pilot programme.

To facilitate comparison across studies in terms of the interpretation of findings to the Irish context, willingness-to-pay (WTP) thresholds of €20,000 and €45,000 per quality adjusted life year (QALY) gained were used (that is, those typically used in Ireland as reference points for decision-making regarding the reimbursement of a technology). For cost-utility analyses, based on adjusted incremental cost-effectiveness ratios (ICERs), screening was considered potentially cost effective, at a WTP threshold of €45,000 per QALY gained, in six of seven studies. The study based on empirical data explored three TREC cut-off strategies, with all three adjusted ICERs being at or below the WTP of €45,000 per QALY.

Through various sensitivity analyses, most studies reported that the models appeared to be sensitive to variations in a number of key variables, including: test specificity, incidence of SCID, screening test costs, diagnostic costs, the cost of

treatment (especially costs of treatment for late detected SCID cases), and survival post treatment.

Given the rarity of the condition, the relatively small birth cohort in Ireland, and limitations in existing data, it is unlikely that a model specific to the Irish context would be of additional value. Many of the parameter estimates to support such a model would need to be sourced from the studies included in this review which is not expected to reduce the uncertainty presented in this review. Overall, the majority of studies indicated that universal TREC-based screening for SCID is potentially cost effective compared with no screening, considering the typical WTP thresholds used in Ireland. However, it should be noted that no study directly considered the cost effectiveness of SCID screening for a scenario where screening for ADA-SCID was already in place, as is the case in Ireland.

If screening for ADA-SCID were to be in place, the incremental benefits would be expected to be lower as a proportion of the cases would already have been detected through such screening. However, the incremental costs would not be expected to be correspondingly lower. This would be expected to result in higher ICERs (that is, it would be less cost effective) than the estimates observed.

Budget impact analysis

A budget impact analysis was undertaken to estimate the incremental budget impact associated with the addition of TREC-based screening for SCID to the current standard of care. The aim of adding TREC-based screening for SCID to the existing NNBSP is to enable early identification of SCID cases who are currently diagnosed based on clinical presentation. Screening also aims to identify any SCID cases not captured by current practice (that is, there may be a number of children who die prior to clinical presentation or diagnosis hereafter referred to as 'undiagnosed').

The analysis was conducted over a five-year time horizon from the perspective of the publicly-funded healthcare system. It was estimated that approximately 58,000 newborns annually would be eligible for screening based on the Central Statistics Office population projections and an NNBSP reported uptake rate of 99.9%. With the exception of the previously undiagnosed population, this analysis considered the cost of management up to the point of HSCT.

The budget impact analysis was undertaken in two parts to reflect costs associated with different parts of the screening programme: verification and implementation of screening (for example, costs associated with laboratory equipment and staffing) and diagnosis and treatment (for example, costs associated with hospital admission or outpatient appointments).

The incremental budget impact associated with verification and implementation of TREC-based screening for SCID was estimated at €3.0 million over a five-year time horizon. The incremental budget impact was driven largely by the cost of the TREC test kit (consumables), equipment and labour. In one-way sensitivity analysis, the budget impact was sensitive to the cost of the TREC test kit which is uncertain. In the base case analysis it was assumed that initial implementation would take place in the current NNBSL in CHI at Temple Street, requiring reconfiguration of the existing laboratory. If implementation were to be deferred until the laboratory at the new children's hospital is operational, first year implementation costs would be approximately €130,000 lower.

The diagnosis and treatment of SCID and non-SCID TCLs identified through TREC-based screening was estimated to result in an incremental budget impact of approximately €660,000 over a five-year time horizon. Earlier diagnosis of SCID cases, who present clinically under current practice, was associated with a partial cost-offset owing to a reduction in resource use and treatment costs for these patients. Under the assumption of an increase in post-screening prevalence, the majority of this incremental budget impact was associated with the identification of a number of children with SCID who would have been undiagnosed in the absence of screening (that is, those who die prior to clinical presentation). Notably, this assumption is subject to a very high level of uncertainty and when explored in scenario analysis was noted to be a significant driver of the budget impact.

If a decision were to be made to implement TREC-based screening for SCID, the outcomes of screening in the Irish context and associated incremental costs would be dependent on the results of verification of the testing method and establishment of population norms.

The total incremental budget impact is therefore estimated at €3.66 million over five years, comprising €3.0 million for verification and implementation and €660,000 for treatment of SCID and non-SCID TCLs. The certainty of the results is limited by the availability of data to consider all relevant clinical and economic consequences. Key uncertainties include the cost of the TREC test kit, the number of abnormal TREC screens, care pathways for non-SCID TCLs and the incidence of undiagnosed SCID.

Organisational aspects of the addition of screening for SCID to the NNBSP

An assessment of the organisational implications of the potential addition of TREC-based screening for SCID to the NNBSP was undertaken, with the work informed by the international literature and engagement with national stakeholders. While it is important to consider individual stakeholders and requirements in detail, it should be

noted that the overall process of adding new conditions to the NNBSP is complex and requires a collaborative and programme-centred approach.

TREC-based screening for SCID would introduce new technology to the NNBSL but would not require a change to the current physical process of sample collection for screening. Furthermore, it is anticipated that the current capacity of the NNBSP (excluding laboratory-specific requirements described below) is expected to suffice should the outlined needs of the current programme, which were submitted as part of the 2023 HSE National Service Plan, be fulfilled. The implementation of TREC-based screening for SCID would require the recruitment of additional laboratory staff to enable its verification and ongoing implementation.

At the time of writing, there is a documented shortage of medical scientists in Ireland which may impact such recruitment. Additionally, new equipment will need to be procured and training provided for laboratory personnel, given that this form of testing, and the associated equipment and technical expertise, is not currently in place in the NNBSL.

The time at which screening is introduced would have important implications for the site of implementation. The NNBSL is scheduled to move to the new children's hospital on the St James's Hospital Campus with extensive ongoing project management and resource requirements associated with this move. If TREC-based screening for SCID were to be implemented at CHI at Temple Street, structural modification of the laboratory would be required to meet the additional physical space requirements for sample preparation and new equipment. The benefits of implementation at this site will need to be considered in light of the upcoming move, taking account of the finite capacity for further project management and the structural work required. It is expected that there will be sufficient physical space for the implementation of this form of screening at the new children's hospital.

The testing method and screening algorithm will need to be established in terms of the defined screening target and establishment of population norms and cut-offs. Specific considerations for the screening algorithm include: the handling of inconclusive results, provisions for infants that are preterm or in intensive care at the time of sample taking, and the sequence of the ADA-SCID screening test relative to the TREC-based screening test. Assay verification, which would be undertaken prior to implementation, would aim to maximise the identification of SCID cases and to minimise the risk of false positives and the detection of non-SCID TCLs of potentially unknown clinical significance. Consistent with standard practice in the NNBSP, following implementation, provisional TREC cut-offs set during assay verification would be reviewed and revised as necessary when evaluating screening outcomes.

If TREC-based screening for SCID is implemented, elements such as the communication of screen results, structure of referral pathways, and management of instances of false positives will need to be considered. In terms of follow-up, for all abnormal results, this would initially take the form of clinical examination and a blood draw. There are established diagnostic and treatment pathways for SCID; however, in the case of false positive results, there would be a need for further communication with parents to relay the false positive finding and to alleviate concerns. For non-SCD TCLs, follow-up would include outpatient attendance for confirmatory testing followed by initiation of clinical care appropriate to the condition detected.

Screening for SCID will also likely detect more cases of non-SCID TCLs than cases of SCID. While many of these non-SCID TCLs may be identified in the absence of screening, there will likely be additional demand for immunology services in terms of referrals for confirmatory diagnosis and follow-up appointments.

The NNBSP has an established quality assurance programme. If TREC-based screening for SCID is implemented, consideration should be given to monitoring and evaluating the continuing relevance of screening for ADA-SCID alongside TREC-based screening. In terms of acceptability, the NNBSP has a notably high uptake rate with near population-wide coverage. While international literature would not suggest that the addition of screening for SCID would lead to a reduction in uptake, this indicator should continue to be monitored through the NNBSP quality assurance processes.

For conditions that meet the evidence bar for inclusion in the NNBSP, consideration of the timing of these additions may provide opportunities to facilitate efficiencies in the verification processes (particularly for conditions which may be screened for using the same technology), training requirements, and programme adjustments. Specifically, there may be efficiencies for the programme associated with deferring implementation to allow for a number of changes to the programme to be made at the one time as opposed to implementing changes sequentially (that is, as soon as a positive recommendation is made). However, efficiencies for the programme would need to be weighed against the individual clinical benefit for children identified through screening.

Ethical and social considerations associated with the addition of newborn screening for SCID

In terms of the benefit-harm balance, this form of screening requires consideration of multiple groups that may be detected by the test. These include those with SCID, those with non-SCID TCLs, and instances of false positives. The benefit-harm

balance varies across these groups. For children with SCID and their families, there are clear benefits associated with the screening in terms of infection prevention and possible access to earlier treatment, which are likely to result in better outcomes. There are also benefits for the childhood immunisation programme in Ireland in terms of maintaining trust and confidence in this programme, given the importance of avoidance of live vaccines in children with SCID. For children with non-SCID TCLs the benefit-harm balance may vary, as not all will be clinically relevant or will benefit from earlier detection. For instances of false positives, there is the potential for psychosocial harm, including stress and anxiety for the family. Additionally, false positive results may require the child to be exposed to additional testing, for example blood tests.

Excessive detection of non-SCID TCLs that are not clinically relevant or of false positives may undermine confidence in the NNBSP. In light of the potential for psychological harm associated with screening results across all groups affected, the approach to communication of abnormal screening results is an important consideration and may be particularly important in the context of false positive results. There is a requirement for information to be provided in a clear, consistent and timely manner.

Regarding autonomy, screening for SCID involves a particularly vulnerable population (newborns) with consent provided by parents, potentially at a time of stress and fatigue in the postnatal period. Obtaining truly informed consent in the context of newborn screening can be challenging given the rarity and complexity of the conditions screened, alongside the intricacy of understanding screening processes. Therefore, there is a need for a careful balance that does not overstate the potential for positive findings while still ensuring the parent is informed of the potential outcomes and impact of screening, particularly when considering the range of non-SCID TCLs that may be detected.

Informed consent is more complex in this context due to the variety of findings that may emerge from screening for SCID, whereas for most other conditions, informed consent is more straightforward. Additionally, the influence of socioeconomic factors and health literacy has an important bearing on how information is provided and translated into parent decision-making.

From the perspective of justice and equity, there is a potential for displaced care and strain on the capacity of the system should this form of screening be implemented, which may not be equitable at the population level. This is particularly relevant when considering the number and types of non-SCID TCLs that may be detected and is further compounded by the uncertainties that exist in the estimates of cost-effectiveness and resource implications associated with screening for SCID.

Finally, in terms of the ethical consequences relating to the conduct of the HTA itself, there are limitations in the evidence available nationally and internationally to inform these types of assessments; many estimates included within the HTA are based on proxies, expert opinion, or are associated with much uncertainty. There are also important considerations relating to the timing of the HTA and the impact on overall findings in light of elements such as the recent addition of ADA-SCID screening to the NNBSP and the ongoing assessment of HSCT repatriation.

Conclusion

SCID is a rare but serious inherited condition which is almost uniformly fatal in the first year of life without appropriate treatment. National and international evidence consistently suggests that earlier identification, and earlier treatment, for SCID results in better clinical outcomes for the child in terms of reduced morbidity and mortality. Early identification of infants with SCID through screening also facilitates the avoidance of live vaccines which can be detrimental to the health of children with SCID.

The addition of TREC-based screening for SCID will further enable the earlier detection of infants who will otherwise present clinically, as well as the potential detection of children who would otherwise experience early mortality prior to a diagnosis being made. While considered sensitive, TREC-based screening for SCID is not specific to SCID. Other TCLs will also be identified, and it is likely that the incidence of these non-SCID TCLs detected through screening would be higher than that of SCID. The testing method and screening algorithm will need to be developed and verified to ensure optimal sensitivity and specificity is achieved.

The incremental budget impact of adding TREC-based screening to the NNBSP was estimated at €3.66 million over five years. This estimate was driven largely by the cost of the TREC test kit, the new equipment and laboratory staff necessary to implement the testing, and the potential for an increase in post-screening prevalence. Notably, the increase in post-screening prevalence is particularly challenging to estimate and is subject to high levels of uncertainty.

Given the scheduled move of the NNBSL to the new children's hospital, the timing of verification and implementation would have important implications as there are already extensive ongoing project management and resource requirements. Implementation prior to the move would necessitate structural reconfiguration of the existing laboratory as well as the additional workload for the laboratory at a time when there is finite capacity for the same. If TREC-based screening for SCID is implemented, consideration should be given to monitoring and evaluating the continuing relevance of screening for ADA-SCID alongside TREC-based screening through the quality assurance programme of the NNBSP.

From an ethical and social perspective, the benefits of screening for children with SCID, their families and the broader health system should be weighed against the potential for harm in the context of instances of false positives and the non-SCID TCLs detected through screening (not all of which will be clinically relevant or will benefit from earlier detection). While the physical harms associated with false positives are relatively minor (with confirmatory tests largely involving a blood draw), there is the potential for anxiety among parents.

Plain Language Summary

The Health Information and Quality Authority (HIQA) was requested to assess potentially screening for severe combined immunodeficiency (SCID) as part of the National Newborn Bloodspot Screening Programme (NNBSP) in Ireland. This assessment gives the National Screening Advisory Committee (NSAC) information to help them make their recommendation on this issue to the Minister for Health.

The overall goal of screening is to provide early treatment or interventions to someone who has been identified with the condition. Ideally this would lead to better outcomes than if the person were to present later with symptoms. Screening of newborns is performed in Ireland through the NNBSP. The current programme looks for nine rare, but serious conditions. The screening is performed by collecting drops of blood from an infant's heel onto a piece of card (also known as 'the heel prick test') and then performing tests on the blood in a laboratory. In the rare event that an abnormal result is found, the child undergoes further testing to see if they do in fact have one of the conditions screened for. If a child is then diagnosed with one of the conditions, they are referred for treatment.

SCID is an inherited condition that impacts on the body's ability to fight infection. The condition can be passed down by one or both parents and results in the child having lower levels of T-cells than normal. T-cells are a type of immune cell that fights infection. Typically, there are no symptoms at birth. A diagnosis of SCID is considered an emergency as the condition almost always results in death in the first year of life unless the child receives treatment. This treatment usually involves haematopoietic stem cell transplantation (HSCT), also known as a bone marrow transplant. This transplant uses stem cells taken from a suitable donor (often a relative). These healthy, donated cells are then given to the child through an intravenous (IV) infusion. The stem cells travel to the bone marrow where they multiply over time. In this way, they can provide the child with a working immune system that is able to fight infection.

In Ireland, between 2005 and 2020, there were 27 children diagnosed with SCID, meaning that about 1 in 40,000 newborns were diagnosed with SCID. Of these cases, half had one specific type of SCID known as ADA-SCID, which occurs at a higher proportion in Ireland than in other countries. The majority of these cases were members of the Irish Traveller community. Screening for ADA-SCID was introduced in Ireland in May 2022. If screening for all types of SCID were adopted, it would help identify those cases of SCID that are not detected through just screening for ADA-SCID.

Outside the new screening programme for ADA-SCID, children with SCID in Ireland are identified by risk-based detection at birth (through family history such as a brother or sister that was previously diagnosed as having SCID) or when they present with symptoms. These symptoms can include severe infections and or issues with the child's overall growth and development. From the Irish data, and from international reports, it appears that those diagnosed on the basis of developing symptoms tend to have more infections, more complications, and are more likely to die compared to those who are diagnosed at birth (on the basis of a family history or screening).

TREC-based screening for SCID involves counting the numbers of a specific product in the blood, called 'T-cell receptor excision circles (TRECs)'. Below a certain number (cut-off point), the test is considered to be an abnormal (or 'positive') test result. The cut-off used is important as it partly decides how many children will be identified as having an abnormal screen result and will need further testing. It is important to note that the TREC-based test does not just identify SCID – it will also identify any other condition that causes an infant to have very low numbers of T-cells; this includes a lot of other conditions that affect the immune system. In order to know whether the low T-cell counts identified during screening are due to SCID or another type of immune condition, further tests are required. We reviewed screening programmes in 34 countries and found that nine countries currently have newborn screening for SCID in place (with three more using it only in certain regions of the country); a number of other countries are exploring whether this screening should be introduced.

A review of studies of international screening programmes was performed to see how well the TREC-based test detects SCID. When looking at these studies, there were some differences in the screening methods used. For example, screening programmes used different cut-offs for when a test was considered to be an abnormal (or 'positive') test result. The review found that TREC-based screening programmes are good at finding newborns with SCID. However, they will also identify other children with a low T-cell count ('T-cell lymphopenia' or 'TCL'). This low T-cell count may be a temporary finding (for example, as may occur in premature babies) or the child may have a different medical condition that results in low T-cell counts (that is, a non-SCID TCL). Not all of these conditions will be clinically important, so it may not always be helpful to identify them. There will also be a number of children who have an abnormal test result, but who do not have SCID or any other cause of TCL - these are called 'false positive' test results. We calculated the number of false positive results that might happen in Ireland in a single year. Based on what was found in the study with the highest rate of false

positive results, we estimated that there could be up to 52 false positive test results per year.

This assessment also reviewed international studies to look at the benefit of early diagnosis and or early treatment compared with late diagnosis and or late treatment in children with SCID. There are some issues with the studies we found, which makes it difficult to make strong statements about the evidence. This is a common challenge for rare conditions such as SCID. However, these studies represent the best available evidence. Overall, they consistently suggested that children who are diagnosed and treated earlier have fewer complications and are less likely to die than children who are identified later.

The assessment also reviewed international studies to understand whether or not screening for SCID is an efficient use of healthcare resources. No study looked at screening for SCID when screening for ADA-SCID is already in place, as is the case in Ireland. However, studies that just compared screening with no screening generally found it to be an efficient use of healthcare funding.

We assessed whether or not SCID screening is likely to be affordable for the Irish healthcare system. Setting up the laboratory and carrying out screening would cost an estimated €3.0 million over five years. The cost of the TREC test kit was an important factor. Treating SCID and other conditions identified through the screening would likely result in additional spending of about €660,000 over five years. However, these extra costs associated with treatment are uncertain, as it is not known if screening will identify more cases of SCID than we currently find every year through other ways (for example, children being diagnosed because of symptoms).

There are a number of challenges in setting up newborn screening for SCID. These challenges include the hiring and training of laboratory (lab) staff to set up and run the testing. The lab where the tests are processed will be moving to the new children's hospital (due to open in 2025). If screening for SCID were to start before this date, the current lab would have to be modified to provide more space. Regardless of where the lab is located, the lab staff would need to refine the methods involved in the screening test itself to make sure that it is performing properly. This is something the lab staff has done with the other tests in the programme.

We examined the ethical and social issues that might come up when considering adding SCID to the newborn screening programme. The importance of providing clear, consistent and timely information to parents at each step was highlighted. Also, issues were identified with finding other conditions, some of which do not have

clear treatments. In making a decision on whether screening for SCID should take place, it is important to think about the different groups, and their families, that may be impacted by such a decision. These include those with SCID, those with other conditions that might be identified through screening (non-SCID TCLs), not all of which will be clinically important or benefit from being identified earlier, and those who have a false positive result (those who have an abnormal test, but do not in fact have SCID or a non-SCID TCL).

List of abbreviations used in this report

ADA	adenosine deaminase
ADA-SCID	adenosine deaminase deficiency severe combined immunodeficiency
AK2	adenylate kinase 2
BCG	Bacillus Calmette–Guérin
BCL	B-cell lymphopenia
BCR	B-cell receptors
BIA	budget impact analysis
CD	cluster of differentiation
CEA	cost-effectiveness analysis
CEREDIH	Centre de Référence Déficits Immunitaires Héréditaires (French national reference centre for primary immunodeficiencies)
CF	cystic fibrosis
CH	congenital hypothyroidism
CHEC	Consensus on Health Economics Criteria
CHI	Children's Health Ireland
CI	confidence interval
CIBMTR	Center for International Bone and Marrow Transplant Research (US)
CMV	cytomegalovirus
CORO1A	coronin 1A
CPD	continuous professional development
CPI	consumer price index
CPSP	Canadian Paediatric Surveillance Program
CSO	Central Statistics
CUA	cost utility analysis
DBS	dried bloodspot
DCLRE1C	DNA cross-link repair 1C
DoH	Department of Health
DRG	Diagnosis-related Group
EAG	Expert Advisory Group
EFS	event free survival
EMA	European Medicines Agency
EBMT	European Group for Blood and Marrow Transplantation
ERT	enzyme replacement therapy
ESID	European Society for Immunodeficiencies
EUnetHTA	European Network for Health Technology Assessment

FDA	US Food and Drug Administration
FOXN1	forkhead box N1
GA1	glutaric aciduria type 1
GALT	classical galactosaemia
G-BA	Federal Joint Committee of Doctors and Health Insurance Funds (Germany)
GP	General Practitioner
GT	gene therapy
GvHD	graft-versus-host disease
HAS	Haute Autorité de Santé (France)
HCU	homocystinuria
HIPE	Hospital Inpatient Enquiry
HIQA	Health Information and Quality Authority
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
HPO	healthcare pricing office
HR	hazard ratio
HSE	Health Service Executive
HSCT	haematopoietic stem cell transplantation
HTA	Health Technology Assessment
ICER	incremental cost-effectiveness ratio
ICU	intensive care unit
IEI	inborn error of immunity
Ig	immunoglobulin
IgRT	immunoglobulin replacement therapy
IL2RG	interleukin 2 receptor gamma chain
IL7Rα	interleukin 7 receptor alpha
INESSS	Institut National d'Excellence en Santé et en Services Sociaux (Quebec, Canada)
IPC	infection prevention and control
IQR	interquartile range
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
IUIS	International Union of Immunological Societies
IVD	*in vitro* diagnostic medical device
IVIG	intravenous immune globulin
JAK3	janus kinase 3
KREC	kappa-deleting recombination excision circles
KPI	key performance indicator

LAT	linker for activation of T cells
LIG4	DNA ligase 4
LRTI	lower respiratory tract infection
LY	life year
MCADD	medium chain acyl-CoA dehydrogenase deficiency
MFD	matched family donor
MHC	major histocompatibility complex
MMFD	mismatched family donor
MMUD	mismatched unrelated donor
MRD	matched related donor
MS/MS	tandem mass spectrometry
MSD	matched sibling donor
MSUD	maple syrup urine disease
MUD	matched unrelated donor
NBS	newborn bloodspot screening
NGS	next generation sequencing
NHEJ1	non-homologous end joining factor 1
NHS	National Health Service
NICU	neonatal intensive care unit
NIH	National Heart, Lung and Blood Institute (US)
NK	natural killer
NNBSL	National Newborn Bloodspot Screening Laboratory
NNBSP	National Newborn Bloodspot Screening Programme
NPV	negative predictive value
NSAC	National Screening Advisory Committee
NSC	National Screening Committee
OS	overall survival
OWSA	one-way sensitivity analysis
PCP	*Pneumocystis* pneumonia
PCR	polymerase chain reaction
PICOS	Population, Intervention, Comparator, Outcomes and Study design
PICU	paediatric intensive care unit
PIDTC	Primary Immune Deficiency Treatment Consortium (US)
PIRD	Population, Index test, Reference test, Diagnosis
PKU	phenylketonuria
PPP	purchasing power parity
PPV	positive predictive value

PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRKDC	protein kinase, DNA-activated, catalytic subunit
PRSI	pay related social insurance
PTPRC	protein tyrosine phosphatase receptor type C
QUADAS-2	Quality Assessment of Diagnostic Accuracy Studies
QALY	quality-adjusted life year
qPCR	real-time quantitative PCR
RAC2	rac family small GTPase 2
RAG	recombination-activating gene
RDI	Rare Diseases Ireland
RCT	randomised controlled trial
SCETIDE	Stem Cell Transplantation for Immunodeficiencies in Europe
SCID	severe combined immunodeficiency
SMA	Spinal Muscular Atrophy
STARD	standards for reporting of diagnostic accuracy
TAS	Treatment Abroad Scheme
TCL	T-cell lymphopenia
TCR	T-cell receptors
TREC	T-cell receptor excision circles
TSH	thyroid stimulating hormone
UCB	umbilical cord blood
URTI	upper respiratory tract infection
USIDNet	United States Immunodeficiency Network
WHO	World Health Organization
VAT	value added tax
WTE	whole time equivalent
WTP	willingness to pay

Glossary

Allogenic HSCT	Allogeneic HSCT is a treatment which involves the transplantation of stem cells (that is, progenitor cells that are capable of differentiating into various types of cells) from a donor to a recipient. It differs from autologous HSCT wherein the patient's own stem cells are used.
Amorphic mutation	A genetic mutation that causes complete loss of gene function.
Antigen	A molecule which stimulates an immune response.
Assay	A laboratory-based test that is typically used to measure the presence, amount, or functional activity of a biological target.
Asymptomatic	Describes a state where an individual has tested positive for or is a carrier of a condition or disease, but does not show symptoms.
Atypical SCID	A form of SCID caused by hypomorphic genetic mutations (see below) in SCID-causing genes and which presents atypically (for example, with higher T-cell counts than expected in typical SCID).
Autosomal recessive	This refers to a genetic pattern of inheritance in which genetic mutations must be passed down by both parents in order for the condition to occur in their child.
Chronic sequelae	Describes secondary adverse health outcomes that occur as a result of a previous event, which last three months or more after recognition, and are distinguishable from health outcomes that initially result from the causative event.
Conditioning regimen	This refers to a series of treatments that a patient may receive in preparation for stem cell transplantation. A conditioning regimen can include monoclonal antibody therapy, chemotherapy, and or radiation therapy.
Confirmatory testing	The testing performed following a positive result on a screening test. Confirmatory testing helps to establish a diagnosis (or to rule out the presence of a condition, meaning that the screening test returned a 'false positive' result) within the context of a screening programme.
Congenital	This refers to a medical condition that is present at or before birth.

Consanguinity	Consanguinity is the sharing of a blood relationship with another person (that is, the people involved are closely related through a common ancestor).
Diagnostic odyssey	The journey from initial presentation with clinical symptoms, examination findings or test results suggestive of a person's condition to receiving a definitive diagnosis. The odyssey may be characterised by its duration and its circuitousness (number of consultations or different specialities involved) from beginning to end. This time can be associated with stress and anxiety for the family alongside delayed intervention for the patient in the absence of a formal diagnosis.
Donor source	This refers to the source from which stem cells are being donated for HCST (for example, bone marrow or umbilical cord blood).
Donor type	This refers to the relationship and degree of matching between the donor and the recipient (for example, related or unrelated, matched or mismatched). Matching refers to how similar one person's cells are to those from another person (see HLA definition below).
Event-free survival	The length of time after a specific treatment (for example, HSCT) during which a person remains free of certain complications or 'events' that the treatment was intended to prevent or delay (for example, severe infection, or death).
Failure to thrive	When an infant experiences growth delays or insufficient weight gain.
False negative	This is a test result which incorrectly indicates that a particular condition or attribute is absent.
False negativity	Describes the number of those with the condition that are incorrectly classified as negative by the index test.
False positive	This is a test result which incorrectly indicates that a particular condition or attribute is present.
False positivity	Describes the number of those without the condition that are incorrectly classified as positive by the index test.
Flow cytometry	A technique used to detect and measure physical and chemical characteristics of a set of cells or particles.
Gene therapy	A therapeutic approach in which a disease-causing gene is replaced with a healthy copy of the gene.

Genetic testing	These are tests that study an individual's DNA sequences. This may be used to identify mutations in genes that are associated with an increased risk of a genetic disorder.
Graft versus host disease (GVHD)	Graft versus host disease (GvHD) is a complication that can occur following an allogeneic HSCT. It involves donor stem cells reacting against and attacking healthy host cells, and can result in severe life threatening damage.
Haematopoietic stem cells	These are immature cells that have the capacity to develop into all types of blood cells.
Human leukocyte antigens (HLA)	Human leukocyte antigens (HLA) are found on the surface of most cells in the body. This HLA network is an important part of the immune system that plays a central role in enabling the immune response to distinguish between foreign substances and normal cells. In donor identification, HLA are the target for matching.
Hypomorphic mutation	A type of genetic mutation in which the altered gene product has a reduced level of activity.
Idiopathic	An idiopathic disease refers to one that has no known cause or originated spontaneously.
Immune reconstitution	In the context of this report, this refers to the recovery of immune cell development and function after HSCT.
Immunodeficiency	This is when the immune system's ability to fight infection is compromised.
Immunosuppression	This is the reduction of the functioning of the immune system.
Kappa-deleting excision circles (KRECs)	Kappa-deleting excision circles (KRECs) are a by-product of DNA formation during B-cell (a cell of the immune system) development in the bone marrow. Similar to measuring TRECs for T-cell disorders, KRECs can be measured to identify B-cell maturation disorders.
Maternal engraftment	The presence of maternal T cells in the peripheral blood of the child following birth.
Molecular testing	A technique of analysing samples such as tissue, blood or bodily fluid, to identify genes, proteins and other molecules which may cause disease.
Negative predictive value (NPV)	Describes the probability that if a person's test result is negative, that they truly do not have the condition.
Omenn syndrome	Omenn syndrome is a particular form of SCID caused by hypomorphic mutations and characterised by symptoms

	such as skin redness, peeling skin, alopecia, chronic diarrhoea, failure to thrive, and enlarged lymph nodes.
Opportunistic infection	These are infections which occur more frequently or are more severe in people with weak or compromised immune systems.
Positive predictive value (PPV)	Describes the probability that when a test result is positive, that the person truly has the condition.
Precursor cells	Sometimes referred to as partially differentiated cells, these are stem cells which have developed to the point where they will develop into a specific cell type, for example, a T-cell.
Real-time quantitative PCR (qPCR)	Real time quantitative polymerase chain reaction (qPCR) is a method by which sequences of DNA (segments of genetic code) can be analysed in real-time by a detector to quantify the amount of that segment of DNA being expressed.
Screening algorithm	The processes and sequence of actions followed in order to detect a specific disease or condition in a population.
Sensitivity	Describes the proportion of those with the condition that are correctly classified as positive by a test.
Specificity	Describes the proportion of those without the condition that are correctly classified as negative by a test.
T cell lymphopenia	A condition in which there is a lower-than-normal number of lymphocytes (cells of the immune system often known as 'white blood cells') in the blood.
T cell proliferation analysis	The measurement or monitoring of the number of T-cell divisions over a set period of time.
T-cell receptor excision circles (TREC)	A by-product of DNA formation during T-cell development in the thymus. As such, they are considered a direct and reliable measure of thymic function.
Typical SCID	A type of SCID characterised by low or absent T cells, resulting in a non-functional immune system.
X-linked SCID	A type of SCID that is caused by a mutation on the X chromosome and is inherited in a recessive manner. As the inheritance is recessive, in males (who have only one X chromosome), one altered copy of the gene in each cell is sufficient to cause the condition. In females (who have two X chromosomes), a variant would have to occur in both copies of the gene to cause the disorder. Therefore, X-linked SCID is almost exclusively found in males.

Background to the NSAC and HIQA work programme

In 2018, the *Scoping Inquiry into the CervicalCheck Screening Programme* by Dr Gabriel Scally ('the Scally Report'),[1] recommended the establishment of a National Screening Committee to advise the Department of Health and the Minister on all new proposals for screening and on revisions to current programmes. Following this report, the National Screening Advisory Committee (NSAC) was established in 2019 by the Minister for Health as an independent advisory committee to play a significant strategic role in the development and consideration of population-based screening programmes in Ireland. At the request of the Department of Health, the Health Technology Assessment (HTA) directorate within the Health Information and Quality Authority (HIQA) undertakes evidence synthesis. HIQA provides evidence-based advice to NSAC on behalf of the Minister for Health.

Following a request from NSAC, the present document summarises the findings of a HTA on the potential addition of severe combined immunodeficiency (SCID) to the National Newborn Bloodspot Screening Programme (NNBSP).

1. Introduction

1.1 Background to the request

Severe combined immunodeficiency (SCID) is an inherited inborn error of immunity affecting cell-mediated and humoral immunity, and constitutes one of the most severe forms of primary immunodeficiency.[2] SCID is caused by genetic mutations and is characterised by T-cell lymphopenia (TCL), that is, an absence, or significantly depleted level, of functioning T-cells. It can further be associated with varying impact on B-cells and Natural Killer cells, depending on the gene affected.[3-5]

Typically presenting asymptomatically at birth, SCID is considered a paediatric emergency that is almost uniformly fatal in the first year of life without appropriate treatment.[5-8] SCID may be identified through screening, family history or symptomatically.[7] Clinically, SCID presents with features such as the infant experiencing recurrent, opportunistic, and often severe infections, failure to thrive, persistent diarrhoea, and oral thrush.[5, 7] Considering treatment, following diagnosis with SCID, immune reconstitution (that is, rebuilding of the immune system) is possible through treatment with haematopoietic stem cell transplant (HSCT) or, in certain subtypes, gene therapy.[5, 7]

Early identification of SCID is also important given the implications for childhood immunisation. Children with SCID should not receive live vaccines (for example, vaccination against rotavirus infection), given the potential for severe illness and mortality. However, given the timing of immunisation schedules, in the absence of screening or known family history, a child may receive such vaccines, to their detriment, prior to being identified as having SCID.[9]

In 2020, the Health Service Executive (HSE) National Newborn Bloodspot Screening Programme (NNBSP) Governance Group formally requested the National Screening Advisory Committee (NSAC) to consider the addition of one specific form of SCID, ADA-SCID, to the NNBSP in Ireland.[10] Ireland has a notably high incidence of ADA-SCID as a proportion of all SCID cases.[6] At a meeting in July 2020, NSAC approved the application and endorsed the addition of ADA-SCID to the list of conditions screened for in the existing NNBSP.[10]

At the time of the recommendation, the NNBSP Governance Group also requested that an assessment be completed of newborn screening for the remaining subtypes of SCID based on the method of quantification of T-cell receptor excision circles (TRECs).

ADA-SCID is caused by mutations in the adenosine deaminase gene, leading to accumulation of metabolic substrates and subsequent impact on the immune system.[11] Given the accumulation of metabolites, ADA-SCID is detectable on dried bloodspot (DBS) samples through tandem mass spectrometry. This approach is also used for a number of metabolic disorders which are currently screened for through the NNBSP.[12] However, tandem mass spectrometry cannot be used to screen for other forms of SCID, for which the generally accepted method of screening involves quantification of TRECs.[5, 6, 13]

In September 2021, at the request of NSAC, Health Information and Quality Authority (HIQA) agreed to undertake a Health Technology Assessment (HTA) on the potential addition of TREC-based screening for SCID to the NNBSP. The potential inclusion of TREC-based screening for all SCID subtypes in the NNBSP is being considered in addition to the existing panel, which includes screening for ADA-SCID using tandem mass spectrometry.

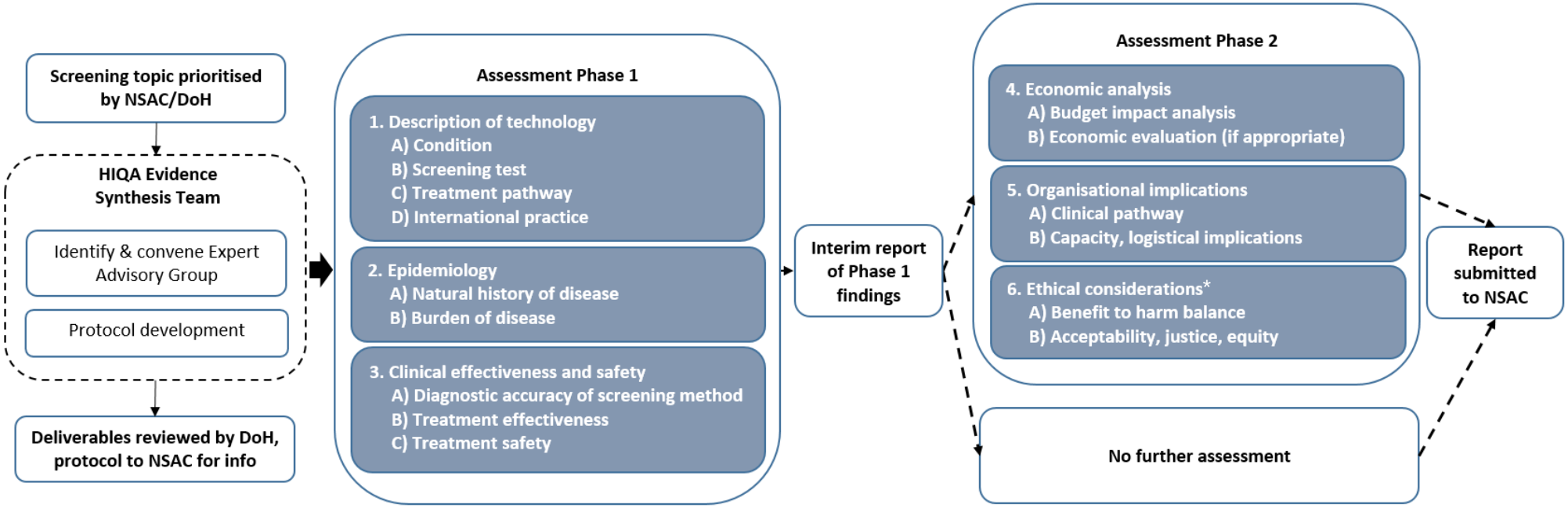
1.2 Overall approach

HTA is a multidisciplinary process that summarises information about the medical, social, economic and ethical issues related to the use of a health technology and does so in a systematic, transparent, unbiased, and robust manner. The HTAs conducted by HIQA's HTA Directorate follow the HTA Core Model® proposed by the European Network for Health Technology Assessment (EUnetHTA).[14] As appropriate to the topic, HTAs may include all, or some, of the following domains:

- description of the technology
- epidemiology
- clinical effectiveness and safety
- costs and economic evaluation
- organisational, social, ethical and medicolegal implications.

HIQA has proposed a stepwise (two-phase) process, as outlined in Figure 1, to this evidence synthesis approach used to inform NSAC advice to the Department of Health. A detailed protocol outlining the methodological approach to this HTA has been published (available here). In the first phase, evidence synthesis was conducted for the domains of the description of the technology, epidemiology, and clinical effectiveness. Following the interpretation of the findings of these HTA domains, in June 2022, a second phase was requested by NSAC to assess the economic, organisational, social, and ethical implications of introducing newborn TREC-based screening for SCID in Ireland.

Figure 1.1 HTA process flow to inform NSAC advice on NNBSP



Key: DoH – Department of Health; HTA – health technology assessment; NBS – newborn screening; NSAC – National Screening Advisory Committee
*May further include social and legal considerations as appropriate.

1.3 Terms of reference

Based on the available evidence, this HTA will inform the decision-making by, and subsequent recommendation of, NSAC to the Minister for Health. As per the approach outlined above, the terms of reference for this HTA, as agreed with the Department of Health, were to:

- Describe the existing and proposed diagnostic and treatment pathway for SCID in Ireland.
- Conduct a review on the international practice of the use of TREC-based screening for SCID.
- Describe the burden of disease associated with SCID in Ireland.
- Perform a review of the test accuracy of TREC-based screening for SCID.
- Perform a review of the clinical effectiveness of early HSCT treatment compared with late HSCT treatment for SCID.
- Evaluate the cost effectiveness of newborn screening for SCID.
- Estimate the resource and budget implications of introducing TREC-based screening for SCID in Ireland.
- Consider any wider organisational, ethical, or societal implications that newborn screening for SCID may have for patients, families, the general public, or the healthcare system in Ireland.
- Produce a report summarising the above pieces of work.
- Convene a meeting of the HIQA EAG, and present the above findings to the EAG for their interpretation and input.
- Subject to HIQA board approval, provide a final report summarising the overall findings of the assessment and HIQA's advice to NSAC.

A multidisciplinary EAG was convened by HIQA comprising representation from relevant stakeholders including the Department of Health, the HSE, the National Immunisation Advisory Committee, the NNBSP, National Newborn Bloodspot Screening Laboratory, clinicians with specialist expertise in paediatric immunology, public health, haematology, and clinical genetics, three patient and public representatives (Irish Primary Immunodeficiencies Association, 22q11 Ireland, and Cuidiú) and methodological experts. The role of the EAG is to inform and guide the process, provide expert advice and information, and to provide access to data where

appropriate. A full list of the membership of the EAG is available in the acknowledgements section of this report.

The terms of reference of the EAG were to:

- Contribute to the provision of high quality research and considered advice by HIQA to NSAC on behalf of the Minister for Health.
- Contribute to the work of the group by providing expert guidance, as appropriate.
- Be prepared to provide expert advice on relevant issues outside of group meetings, as requested.
- Provide advice to HIQA regarding the scope of the analysis.
- Review the project plan outline and advise on priorities, as required.
- Support the Evaluation Team during the assessment process by providing expert opinion and access to pertinent data, as appropriate.
- Review the draft report from the Evaluation Team and recommend amendments, as appropriate.
- Contribute to HIQA's development of its approach to HTA by participating in an evaluation of the process on the conclusion of the assessment.
- Notify the project lead if a nominee can no longer participate or contribute to the process, as non-participation may require alternative EAG membership to be sought.

HIQA appointed an Evaluation Team, comprising staff from the team within the HTA Directorate designated to support NSAC, to carry out the assessment.

The Terms of Reference of the HTA were reviewed by the EAG at its first meeting. The draft description of technology, epidemiology, systematic review of TREC-based newborn screening for SCID and systematic review of the clinical effectiveness of early versus late HSCT were discussed at that meeting. Consideration of the economic, organisational, social, and ethical implications were discussed at a second meeting of the group. Draft versions of this report were circulated for review by the EAG and amended as appropriate. Consistent with standard HIQA governance, the final draft of the HTA was submitted to the Board of HIQA for approval. Following its

approval, the finalised HTA was submitted to NSAC for consideration and published on the HIQA website.

2. Description of the technology

Key points

- This assessment considers the addition of severe combined immunodeficiency (SCID) to the National Newborn Bloodspot Screening Programme (NNBSP) in Ireland using T-cell receptor excision circles (TREC)-based analysis of newborn dried bloodspot samples. This chapter details the current NNBSP, diagnostic and treatment pathways for SCID, and the mechanism, and international use, of TREC-based screening for SCID.
- The NNBSP is offered to all newborns born in Ireland within the first 72 to 120 hours of life. Screening is performed through the collection of a dried bloodspot sample (the 'heel-prick test'), with samples tested at the National Newborn Bloodspot Screening Laboratory (NNBSL). The current programme screens for nine conditions.
- Screening for ADA-SCID (one specific type of SCID) using tandem mass spectrometry was implemented by the NNBSL in May 2022. The potential inclusion of TREC-based screening for all SCID subtypes is being considered in addition to the existing panel.
- SCID is an inherited inborn error of immunity resulting from mutations in at least 19 known genes and which **impedes normal T-cell development**. The condition is typically characterised by T-cell lymphopenia (TCL), that is, lower than normal T-cell counts, with varying impact on B-cells and natural killer cells, depending on the gene affected.
    - Typically presenting asymptomatically at birth, SCID is considered a paediatric emergency. The condition is almost uniformly fatal in the first year of life without appropriate treatment.
    - There are important interactions with the childhood immunisation schedule whereby children with SCID should not receive live vaccines (for example, rotavirus); however, given the timing of immunisation schedules, in the absence of screening or known family history, a child may receive such vaccines prior to being identified as having SCID.
- In the absence of screening, detection of SCID relies on identification through:

- **risk-based detection**, which involves lymphocyte measurement at birth in those with a positive family history (typically a sibling previously diagnosed).
- **clinical presentation** (typically through the development of infections).

- Newborn screening for SCID is possible through the **quantification of TRECs**; this form of analysis is the generally accepted method of screening for SCID internationally.
  - TRECs are a DNA by-product produced during normal T-cell development. The quantification of TRECs in an infant's blood, by way of analysis of a dried bloodspot sample using real-time quantitative polymerase chain reaction (PCR), provides a surrogate marker of thymic output of newly formed T-cells. An absence, or depletion, of TRECs is indicative of TCL.
  - Up to the time of writing, two commercially available kits for TREC quantification have been identified, namely: the Perkin Elmer EnLite™ Neonatal kit and the Immuno IVD SPOT-it™ screening kit (formerly, the SCREEN-ID neonatal screening kit).
  - Given the mechanism of the test, TREC-based screening identifies infants who may have TCL and who require further evaluation. As SCID represents just one cause of TCL, other congenital and secondary causes of TCL, idiopathic TCL, and transient instances of TCL (such as with preterm infants) will be identified through this screening method.
  - The use of combined TREC and kappa-deleting recombination excision circle (KREC)-based screening has been described in the literature.
    - Low KRECs are indicative of B-cell lymphopenia and may be used to identify children with conditions such as X-linked agammaglobulinemia, with some limited evidence to suggest further benefit in the identification of delayed-onset ADA-SCID.
- International **diagnostic guidelines** exist for SCID with the criteria for diagnosis relying on T-cell quantification (generally through flow cytometry). Subsequent tests which may be required as part of the diagnostic pathway include analysis of T-cell proliferation, maternal engraftment studies (that is, a

test for the presence of maternal T-cells), and molecular testing for specific genetic mutations.

- International **treatment guidelines** for SCID are available and are followed in Ireland. Allogeneic haematopoietic stem cell transplant (HSCT) is the primary treatment for SCID and is considered to be potentially curative as it can result in immune reconstitution, though non-immunological symptoms of SCID may remain, depending on the SCID subtype involved.
    - Children's Health Ireland at Crumlin acts as the national tertiary referral centre in Ireland and manages the child before and after HSCT. Currently, the transplantations largely take place in Great North Children's Hospital in Newcastle upon Tyne, United Kingdom.
    - Specifically in the case of ADA-SCID, additional treatment options exist in the form of gene therapy and enzyme replacement therapy (the latter is considered a bridging therapy prior to HSCT).
        - Gene therapy for ADA-SCID is currently only available as a licensed treatment (Strimvelis®) in Milan, Italy. However, gene therapy for ADA-SCID has been used to treat a limited number of ADA-SCID patients from the Republic of Ireland as part of clinical trials at the Department of Paediatric Immunology and Gene Therapy in Great Ormond St. Hospital National Health Service Trust, London.
- A review of **international screening practice** was undertaken to understand the status of screening for SCID internationally. This review examined 34 countries considered to be of most relevance to Ireland from the perspective of screening practice, including those in the European Economic Area, the United Kingdom, the United States, Canada, Australia and New Zealand.
    - Internationally there has been a move towards introducing newborn screening for SCID. As of September 2022, screening was noted to be fully implemented in seven countries in Europe, alongside New Zealand and the United States. Regional implementation, ongoing implementation, piloting, and current review of the potential for screening were noted in nine additional countries investigated.
    - While the majority of newborn screening programmes for SCID involved TREC-based screening, four countries were noted to use combined TREC- and KREC-based screening.

- No clinical pathways or guidelines were identified for the management of non-SCID TCLs detected during newborn screening from these international sources.

The purpose of this chapter is to describe key elements of the technology under consideration. The aims and principles of general screening programmes are first outlined followed by details of the current NNBSP in Ireland. The diagnostic pathway and treatment pathway for SCID are presented, followed by an overview of TREC-based screening, and the status of newborn screening for SCID internationally.

2.1 Screening programmes

Screening is used to identify individuals from an apparently healthy, asymptomatic, population who are at higher risk of a particular condition.[15] The overall aim of screening is the provision of an early treatment or intervention and hence, ideally, better outcomes than if the individual presented symptomatically or later in the disease course.[15] According to the World Health Organization (WHO), the overall aims of a screening programme should be to:[15]

- reduce mortality by early detection and early treatment of a condition
- reduce the incidence of a condition by identifying and treating its precursors
- reduce the severity of a condition by identifying people with the condition and offering effective treatment
- increase choice by identifying conditions or risk factors at an early stage in a life-course when more options may be available.

Rather than comprising an isolated test, screening typically involves a detailed pathway, which includes:

- the identification of a population eligible for screening
- invitation for screening and information provision
- testing
- communication and referral of screen positive results
- diagnosis
- intervention
- treatment and follow-up

- reporting of overall outcomes of the screening programme.[15]

There are a number of considerations that need to be taken into account within decision-making for screening programmes. In October 2020, National Screening Advisory Committee (NSAC) produced a modified list of 20 criteria for appraising the viability, effectiveness and appropriateness of a screening programme.[16] These criteria are presented in Appendix 2.1 in a categorised format (that is, under the headings of 'condition', 'screening method', 'intervention', 'screening programme', and 'implementation').

2.2 The National Newborn Bloodspot Screening Programme in Ireland

The National Newborn Bloodspot Screening Programme (NNBSP) in Ireland is a population-based screening programme which currently screens for nine rare but serious conditions. The governance and organisation of the NNBSP is outlined in Appendix 2.2, with newborn bloodspot screening (NBS) and the NNBSP in Ireland described in detail in a previous Health Information and Quality Authority (HIQA) report.[17] The programme uses NBS based on a dried bloodspot (DBS) sample, which is offered to all newborns in the first 72 to 120 hours of life.

2.2.1 Current conditions screened for by NNBSP

Newborn screening began in Ireland in 1966 and currently screens for nine conditions as outlined in Table 2.1.[18] Screening for ADA-SCID was most recently introduced (May 2022). The remaining subtypes of SCID are not currently screened for by the NNBSP in Ireland.

Table 2.1 Conditions screened for by NNBSP

Condition screened	Estimated Irish incidence
phenylketonuria (PKU)	1 in 4,500
homocystinuria (HCU)	1 in 69,400
maple syrup urine disease (MSUD)	1 in 155,200
classical galactosaemia (GALT)	1 in 16,200
congenital hypothyroidism (CH)	1 in 2,300
cystic fibrosis (CF)	1 in 2,300
medium chain acyl-CoA dehydrogenase deficiency (MCADD)	1 in 66,000
glutaric aciduria type 1 (GA1)	1 in 54,000
ADA-SCID	1 in 78,500

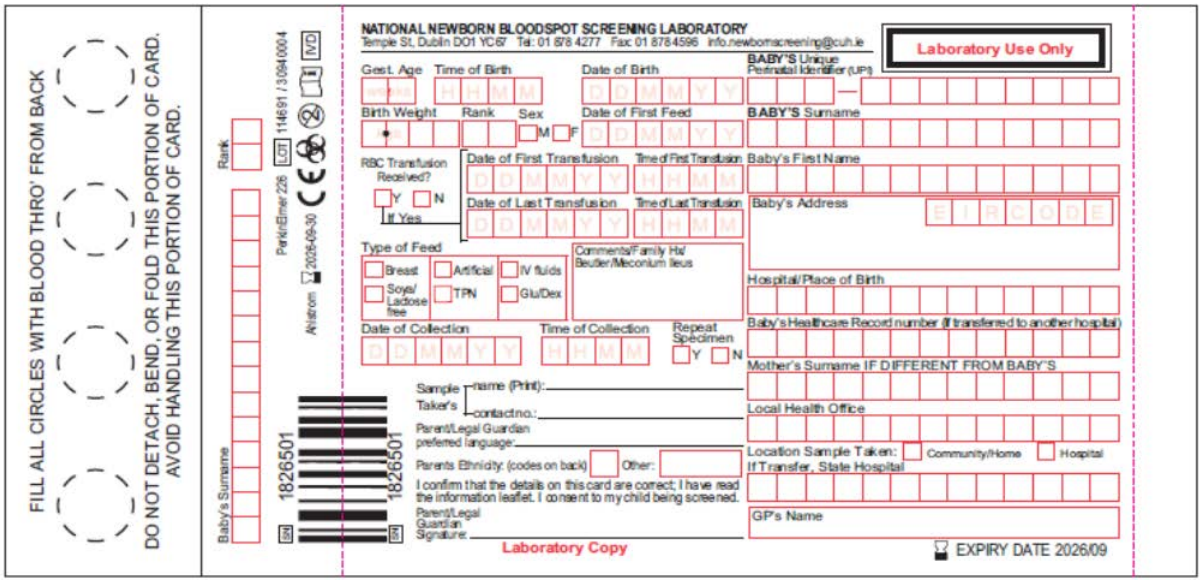
Source: Practical Guide to Newborn Bloodspot Screening in Ireland.[18]

2.2.2 NBS test

With parental or legal guardian consent, the NNBSP involves the collection of a DBS sample, also known as a 'heel prick test', whereby droplets of blood from the infant's heel are collected on a screening card (Figure 2.1). On rare occasions, samples may be collected from a central line (that is, a percutaneous central venous catheter) in ill infants. The sample is usually collected by a midwife or public health nurse, in the first 72 to 120 hours after birth.[18] The lower limit of 72 hours reflects the requirement for the infant to have an adequate protein and galactose intake prior to sample collection, and the fact that thyroid stimulating hormone (TSH) levels may be transiently elevated in the infant in the first days since birth, which complicates the detection of congenital hypothyroidism.[18] Limited exceptions exist to the lower bound time limit in which early sample collections are deemed necessary, and include infants known to be at risk of classical galactosaemia (GALT), those who require blood transfusions, and those with family histories of metabolic conditions; however, a second routine collection is still completed between 72 and 120 hours. The upper bound of 120 hours reflects the need to complete screening prior to clinical presentation given the early and severe onset of certain conditions such as maple syrup urine disease (MSUD) and medium chain acyl-CoA dehydrogenase deficiency (MCADD).

Sample quality is an important consideration, with insufficient, wet, oversaturated, or contaminated samples typically being unsuitable for analysis and requiring a second sample to be collected. Following collection of the sample, the screening card is air dried prior to being placed in a designated envelope and transferred by registered post or courier to the National Newborn Bloodspot Screening Laboratory (NNBSL) at the Children's University Hospital (CHI), Temple Street for processing and analysis.

Figure 2.1 NBS screening card



Source: Practical Guide to Newborn Bloodspot Screening in Ireland.[18]

2.2.3 Laboratory processes

Once processed at the NNBSL, bloodspot cards undergo various analyses depending on the target condition being tested.[18] Five of the conditions screened for in the NNBSP are currently analysed using tandem mass spectrometry, (MS/MS). They are, phenylketonuria (PKU), homocystinuria (HCU), MSUD, glutaric aciduria type 1 (GA1), MCADD, and ADA-SCID.

Should an unclear result be presented or an insufficient sample be noted, a second sample may be requested. A repeat sample may be requested by the NNBSL for a number of reasons, including:[18]

- insufficient sample for all or some of the analyses to be undertaken
- unsatisfactory sample quality (such as, diluted samples, the presence of serum rings, or signs of contamination)
- abnormal, unclear or equivocal results
- sample collection prior to 72 hours after birth
- sample not sufficiently dry prior to transport
- uncertainty regarding the identification of the baby
- expired sample card

- sample received at the NNBSL greater than 14 days after collection
- name on the bloodspot portion of the card does not match that on the demographic section
- sample taken within 72 hours of a red blood cell transfusion.

Results are typically processed, analysed and reported within two days of receiving the sample at the NNBSL.[18] Results of the screening test are transmitted electronically to the hospital, local health office, and referral or tertiary hospital if the baby has been transferred to such care.

2.2.4 Notification of result, and follow-up

As of the time of writing, if no condition is detected, then the parent(s) or legal guardian(s) is not directly contacted.[19] Electronic reports are sent from the laboratory to the Public Health Nursing teams who provide community care for babies and new mothers. If an abnormal result is presented, the Clinical Liaison Officer or Director in the NNBSL contacts a designated liaison nurse or medical registrar in the maternity unit or hospital by telephone.[18] The parent(s) or legal guardian(s) of the infant with a suspected positive screen are contacted directly by telephone, typically by the maternity unit or hospital.[18] The procedure for notification varies somewhat depending on the condition presented. With the parent(s) or legal guardian(s), it is arranged for the baby to be brought directly to CHI at Temple Street, CHI at Crumlin, or to the local Paediatric Unit as requested by the NNBSL.[18] Diagnostic and treatment pathways are then initiated as appropriate to the condition detected.

2.2.5 Detection and uptake rates

Annually, the NNBSP identifies approximately 110 infants with one of the outlined conditions, with notably high national participation in the programme at an estimated 99.9%.[19]

2.3 Severe combined immunodeficiency (SCID)

The condition of relevance to this assessment is SCID. This section provides a brief background to the condition, followed by the associated diagnostic and treatment pathways for SCID in Ireland. The condition will be discussed in further detail in chapter three.

Primary immunodeficiency describes a heterogeneous group of disorders associated with depleted or absent function in one or more components of the immune system.[20] Primary immunodeficiency differs from secondary immunodeficiency in

that the latter results from external factors, such as viral infections, malnutrition or immunosuppressive drug therapy.[20] Most cases of primary immunodeficiency involve inherited disorders, however, acquired forms have also been described within the literature.[20]

SCID is an inherited inborn error of immunity constituting one of the most severe forms of primary immunodeficiency.[2, 7] SCID is typically characterised by T-cell lymphopenia (TCL) with varying immunophenotypes, which depend on which other immune markers are affected, including B-cells and natural killer cells.[2, 3] As will be detailed in chapter three, SCID results from mutations in at least 19 known genes, which gives rise to a large number of subtypes.[2, 21]

2.3.1 Normal T-cell and B-cell development

T-cells are a cornerstone of the adaptive immune response.[22] Originating from haematopoietic stem cells in the bone marrow, precursor cells (that is, cells that may eventually develop into T-cells) migrate to the thymus gland to undergo selection and maturation.[23] T-cells recognise antigens through T-cell receptors (TCR). TCRs are diversified in the thymus through recombination, in which random, repeated rearrangements of variable (V), diversity (D), and joining (J) gene segments produce a diverse group of TCRs.[13, 24] When expressed, these VDJ recombinant TCR genes encode receptor molecules, generating T-cells that can bind appropriately to various antigens encountered.[13] T-cells mature and develop into different types including CD8+ cytotoxic T-cells and CD4+ helper T-cells.[22] Cytotoxic CD8+ T-cells function through a direct recognition by the TCR of a specific antigen, resulting in binding to, and destroying of, the target cell.[22] In contrast, helper CD4+ T-cells, which differentiate into many subtypes, activate when specific molecules are encountered; these cells then function by stimulating other lymphocyte cells (such as T-cell subsets and B-cells).[22]

Like T-cells, precursors for B-cells originate from haematopoietic stem cells; however, B-cells complete most of their development in the bone marrow.[22] B-cell activation occurs when the B-cell receptor (BCR) binds to a specific antigen, through T-cell dependent or T-cell independent activation, and function by producing antibodies.[22]

2.3.2 Clinical presentation

Typically presenting asymptomatically at birth, SCID is considered a paediatric emergency which is almost uniformly fatal in the first year of life without appropriate treatment.[5-8] Clinically, in the absence of early risk-based detection or screening, SCID presents at approximately three to six months, at which point the protective effect of transferred maternal immunoglobulin during gestation and breastfeeding

reduces.[5, 25, 26] Due to the absence, depletion, or dysfunction of T-cells, the infant may present with recurrent and often severe infections, failure to thrive, persistent diarrhoea, and or oral thrush.[5, 7, 24, 27] In addition to more common bacterial and viral infections such as *Streptococcus pneumoniae*, cytomegalovirus and adenoviruses, infants with SCID are also susceptible to opportunistic organisms such as *Pneumocystis jirovecii* (this infection commonly known as 'PCP').[25]

Certain forms of SCID may result in specific additional symptoms. For example, Omenn syndrome, a particular form of SCID, is specifically associated with desquamating erythroderma in the first year of life (as a result of oligoclonal expansion of activated autologous T-cells that affect the skin).[21, 27] ADA-SCID can be associated with marked neurological and cognitive abnormalities, as it is associated with a build-up of metabolites that can result in multiple organ pathologies.[25]

In addition to symptoms resulting from infections, there are important implications of SCID for early childhood immunisation programmes; children with SCID should not receive live viral or bacterial vaccines (for example, Bacillus Calmette–Guérin (BCG) and rotavirus), given the potential for severe illness and mortality.[9, 28] However, given the timing of vaccination schedules, in the absence of screening or known family history, a child with SCID may receive such a live vaccine prior to being recognised as having immunodeficiency, which may result in harm to the child.[9, 25, 28] Specifically in Ireland, the first dose for the rotavirus vaccine is recommended to be given at two months of age, which would typically be before the onset of clinical symptoms for a patient with SCID.[29]

While SCID typically presents symptomatically in the first few months of life, atypical SCID, which occurs when a gene product exhibits reduced rather than absent activity, may present later in life. In particular, a portion of ADA-SCID cases are associated with delayed-onset (typically diagnosed between years one and ten) and late-onset (typically diagnosed after age ten years) presentations.[30] These forms of ADA-SCID are characterised by progressive immunodeficiency that leads to recurring severe infections, immune dysregulation, and organ damage associated with metabolite accumulation.[11, 30, 31] The infections experienced by those with delayed- and late-onset ADA-SCID commonly include recurrent upper respiratory tract infections. While these forms of infections are initially less severe than those occurring in infants with ADA-SCID, progression and accumulation of infections can result in chronic sequelae and autoimmune phenomena before a formal diagnosis is made.[11, 30, 31]

2.3.3 Diagnosis

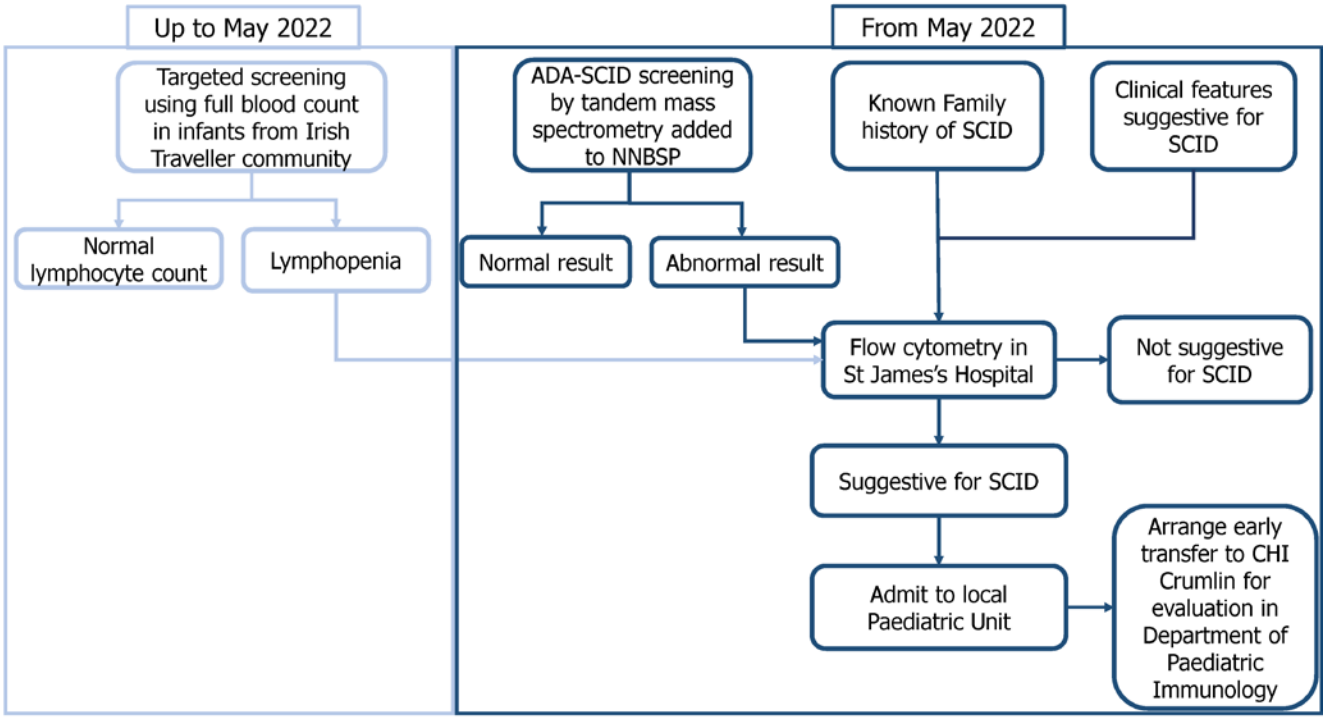
A high-level schematic of the current diagnostic pathway for children with SCID in Ireland is presented in Figure 2.2. Up to May 2022, recognition and subsequent diagnosis of SCID relied on risk-based detection at birth or symptomatic presentation (as described above).[6] Risk-based detection at birth involved identification based on family history (typically a sibling having been diagnosed with the condition) or targeted screening, using full blood counts, for infants of mothers identifying as members of the Irish Traveller community.[32] The targeted screening reflected a formal recommendation in late 2016 by the Neonatal Advisory Committee of the Faculty of Paediatrics in the Royal College of Physicians of Ireland; this recommendation was made given the notable prevalence of ADA-SCID in the Irish Traveller community.

Since May 2022, universal ADA-SCID screening has been implemented in Ireland; however, for the remaining SCID subtypes, identification continues to rely on risk-based detection at birth or symptomatic presentation. The potential inclusion of TREC-based screening for all SCID subtypes in the NNBSP would be in addition to the existing panel, which includes ADA-SCID screening using tandem mass spectrometry.

Flow cytometry at birth is offered to children with a known family history of SCID and those for whom there is clinical suspicion of SCID based on symptoms. If SCID is suspected following flow cytometry, the child is referred to the Department of Paediatric Infectious Diseases and Immunology, CHI at Crumlin, Dublin, which is the national tertiary referral centre for children with suspected inborn errors of immunity.[6] Immunological investigations are performed and the results of these tests are considered against diagnostic criteria; these investigations and criteria are detailed below.

Following a diagnosis of SCID in Ireland, parents are offered genetic screening to identify carrier status, and genetic counselling to understand the impact of such status on their family planning.

Figure 2.2 Diagnostic pathway for children with SCID in Ireland



Source: CHI Crumlin Consultant Paediatric Immunologist.[32]

Immunological investigations

The diagnosis of SCID is established using immunological testing; this may include routine blood tests, flow cytometry, T-cell proliferation analysis, maternal engraftment analysis, and molecular testing for specific mutations, as appropriate.[6]

Flow cytometry is used alongside routine blood tests to quantify the number of T-cells, B-cells and natural killer cells in the infant's blood.[6] Reference values for lymphocytes in those aged zero to three months and those aged three to six months are outlined in Table 2.2.[33] This laboratory-based analysis provides a rapid means of testing the lymphocyte composition in a blood sample by calculating the number of single cells or particles in a sample as they flow past a laser while suspended in a solution.[34]

Within immunology, flow cytometry is most commonly used for immune-phenotyping (that is, identifying specific cells based on the types of proteins expressed on the surface of the cells).[34] As part of the analysis, fluorochrome-conjugated antibodies that are targeted to antigens (for example, CD3 and CD4) on the cell surface are used to stain the cells to facilitate the identification of the different cell types.

In addition to immune-phenotyping, flow cytometry may also be used in this way to analyse the presence of other cell markers, for example, markers of T-cell activity.[34]

The pattern of presence and activity of T-cells, as measured using flow cytometry, can help to indicate the presence of specific forms of SCID. For example, atypical SCID and Omenn syndrome are types of SCID which may not exhibit the extensive T-cell lymphopenia observed with typical SCID but instead involve the presence of T-cells that lack the functionality required for a normal T-cell immune response.(27)

Table 2.2 Reference values for counts of peripheral blood lymphocytes in healthy children

Lymphocyte marker	Reference for 0-3 months (counts per microlitre, 10^{-3})*	Reference for 3-6 months (counts per microlitre, 10^{-3})*
Total lymphocytes	5.40 (3.40-7.60)	6.30 (3.90-9.00)
Total T-cell	3.68 (2.50-5.50)	3.93 (2.50-5.60)
Helper T-cell	2.61 (1.60-4.00)	2.85 (1.80-4.00)
Cytotoxic T-cell	0.98 (0.56-1.70)	1.05 (0.59-1.60)
B-cell	0.73 (0.30-2.00)	1.55 (0.43-3.00)
NK cell	0.42 (0.17-1.10)	0.42 (0.17-0.83)

*Medians (10^{th} and 90^{th} percentiles)
Source: Shearer et al.(33)

T-cell proliferation analysis is used to assess T-cell activity. The analysis is performed through the measurement of in vitro proliferation of T-cells in response to the mitogen phytohaemagglutinin.(25) In healthy individuals, phytohaemagglutinin stimulates the activity of TCRs on T-cells, resulting in signalling that brings about cell division. In contrast, children with SCID typically present with low or absent responses.(35)

Considering **maternal engraftment analysis**, maternal engraftment is a complication which occurs where there is a proliferation of maternal T-cells in the absence of infant T-cells; while immunocompetent newborns rapidly recognise and reject the (human leukocyte antigens (HLA)-mismatched) maternal lymphocytes that pass through the placenta, newborns with SCID fail to reject these circulating maternal T-cells, resulting in the proliferation of these cells.(36, 37) The complication of maternal engraftment occurs to varying extents in infants with SCID, and its presence can have significant implications for diagnosis and treatment.(37) For example, maternal engraftment may impede diagnosis where the maternal T-cells may disguise the lack of the infant's own T-cells. As will be discussed further under diagnostic criteria, if maternal engraftment has been excluded, the presence of T-cell activity may indicate atypical forms of SCID. Considering the clinical impact of maternal engraftment, for children who proceed to haematopoietic stem cell transplant (HSCT), the presence of maternal T-cells can induce graft-versus-host-disease (GvHD) and cause further complications for treatment.(37) Maternal

engraftment is assessed by using polymerase chain reaction (PCR) based techniques to identify maternal DNA sequences.

Following the above analyses, **molecular testing to investigate particular genetic mutations** associated with SCID can be conducted. For the most part, molecular testing for children with suspected SCID in Ireland is directed to Great Ormond Street Molecular Genetics Laboratory in London.[6] Gene sequencing is performed to demonstrate the presence of mutations in one of the known SCID genes, and can provide diagnostic confirmation of SCID and opportunities for genetic counselling.[25]

Diagnostic criteria

Diagnostic criteria for SCID have been developed by the European Society for Immunodeficiencies (ESID) Clinical Working Party,[21, 38] and separately by the US-based Primary Immune Deficiency Treatment Consortium (PIDTC)[39], and are used in Ireland. These diagnostic criteria for **SCID** are outlined in Table 2.3. As highlighted in the table, the ESID provide separate criteria for the diagnosis of X-linked and non X-linked SCID (see section 3.1 under epidemiology for further explanation), with further differentiation relating to definitive, probable, and possible diagnosis.[38]

Differential diagnoses outlined by the ESID Clinical Working Party for non X-linked SCID include, human immunodeficiency virus (HIV) infection, congenital rubella, DiGeorge syndrome, Zap70 deficiency, CD3 deficiency, cartilage hair hypoplasia, MHC class II deficiency, and PNP deficiency. Differential diagnoses for X-linked SCID include JAK3 deficiency, IL7Rα deficiency and HIV.[38]

Both the ESID and the US PIDTC further outline diagnostic criteria for **atypical SCID and Omenn syndrome** as presented in Table 2.4.[21, 39] Patients diagnosed with ADA-SCID through the standard immunological criteria for SCID may also undergo biochemical testing to confirm ADA deficiency. These criteria include elevated plasma deoxyadenosine (> 1µmol/L), and absent or severely deficient (<2% normal) red blood cell ADA enzyme activity. Such testing for Irish patients is carried out in the Purine Research Laboratory at St Thomas's Hospital in London.[6]

Table 2.3 ESID Clinical Working Party and Primary Immune Deficiency Treatment Consortium diagnostic criteria for SCID

ESID Clinical Working Party	Primary Immune Deficiency Treatment Consortium
Definitive diagnosis (non X-linked) Male or female patient less than two years of age with **either** a) engraftment of trans-placental-acquired maternal T-cells; **or** b) less than 20% CD3+ T-cells, an absolute lymphocyte count of less than 3,000/mm^3 **and** at least one of the following: ▪ mutation in the cytokine common gamma chain ▪ mutation in JAK3 ▪ mutation in RAG1 or RAG2 ▪ mutation in IL7Ra ▪ ADA activity of less than 2% of control or mutations in both alleles of ADA ***Probable diagnosis (non X-linked)*** Male or female patient less than two years of age with less than 20% CD3+ T-cells, an absolute lymphocyte count of less than 3,000/mm^3 and proliferative responses to mitogens less than 10% of control; or the presence of maternal lymphocytes in the circulation. ***Definitive diagnosis (X-linked)*** Male patient with either a) engraftment of trans-placental-acquired maternal T-cells; or b) less than 10% CD3+ T-cells, less than 2% CD16/56+ NK-cells and more than 75% CD19+ B-cells, who has one of the following: ▪ mutation in the cytokine common gamma chain (gc) ▪ absent gc mRNA on northern blot analysis of lymphocytes ▪ absent gc protein on the surface of lymphocytes or lymphocyte cell lines ▪ maternal cousins, uncles or nephews with severe combined immunodeficiency. ***Probable diagnosis (X-linked)*** Male patient with less than 10% CD3+ T-cells, less than 2% CD16/56+ NK-cells and more than 75% CD19+ B-cells who has all of the following: ▪ onset of failure to thrive before one year of age ▪ serum IgG and IgA more than two standard deviations below normal for age ▪ persistent or recurrent diarrhoea, URTI or thrush. ***Possible diagnosis (X-linked)*** Male patient with greater than 40% CD19+ B-cells in the peripheral circulation and one of the following: ▪ engraftment of trans-placental-acquired maternal T-cells ▪ maternal cousins, uncles or nephews with a history of severe combined immunodeficiency.	Absence or very low number of T-cells (CD3 T-cells <300/µL) **And** No or very low T-cell function (<10% of lower limit of normal) as measured by response to phytohaemagglutinin **Or** T-cells of maternal origin present

Key: ESID European Society for Immunodeficiencies, mRNA – messenger ribonucleic acid, gc – gamma chain, IgG immunoglobulin G, IgA – immunoglobulin A, URI – upper respiratory tract infection, SD – standard deviation

Sources: ESID[38] and Primary Immune Deficiency Treatment Consortium[39]

Table 2.4 ESID Clinical Working Party and Primary Immune Deficiency Treatment Consortium diagnostic criteria for atypical SCID and Omenn syndrome

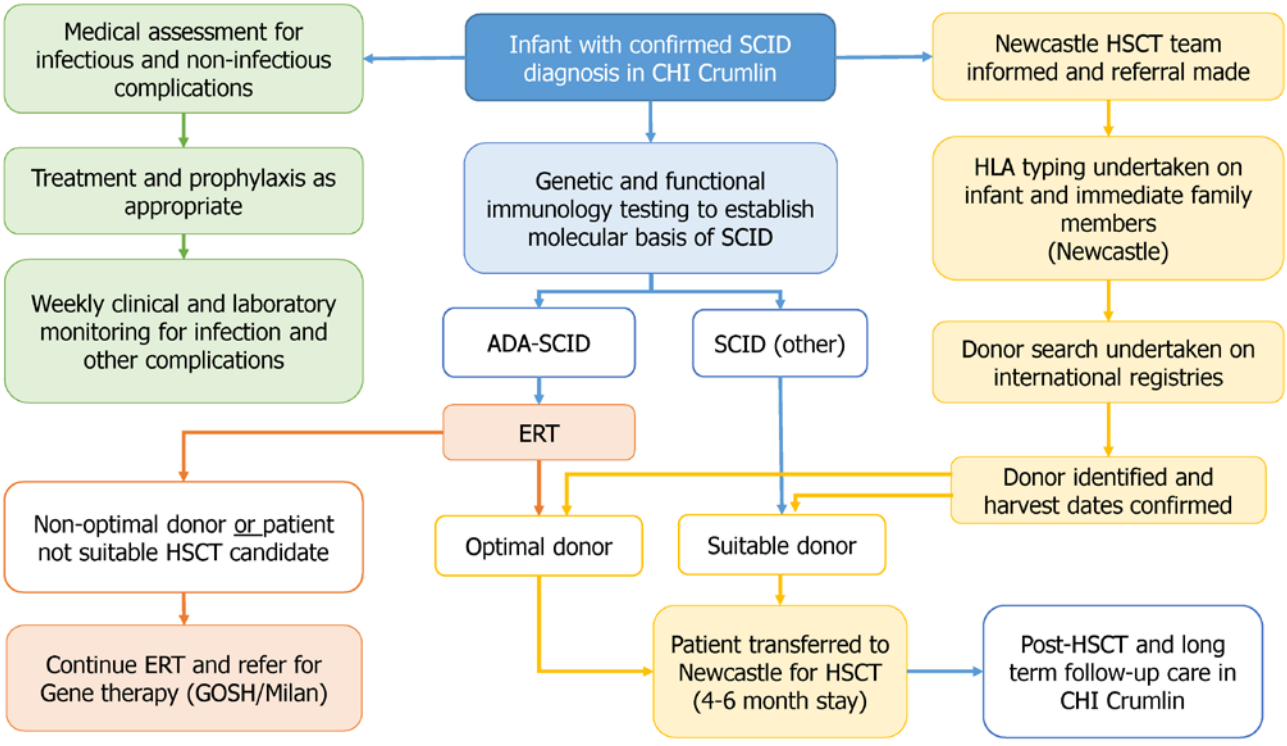
ESID Clinical Working Party	Primary Immune Deficiency Treatment Consortium
Atypical SCID	
Mutation in a SCID-causing gene **And** >100 T-cells/µl **And** Absence of characteristic SCID-associated infections (*Pneumocystis* pneumonia, symptomatic CMV, persistent respiratory or gastrointestinal virus infection) in the first year of life **And** Does not fulfil the criteria for Omenn syndrome	Reduced number of CD3 T-cells ▪ for age up to two years <1,000/µL ▪ for > two years up to four years <800/µL ▪ for over four years <600/µL **And** Absence of maternal engraftment **And** < 30% of lower limit of normal T-cell function (as measured by response to phytohaemagglutinin)
Omenn syndrome	
Desquamating erythroderma in the first year of life **And** One of the following: ▪ lymphoproliferation ▪ failure to thrive ▪ chronic diarrhoea ▪ recurrent pneumonia. **And** Eosinophilia or elevated IgE **And** T-cell deficiency (low naïve cells, reduced proliferation, oligoclonality) **And** Maternal engraftment excluded **And** HIV excluded	Generalised skin rash. **And** Absence of maternal engraftment. **And** Detectable CD3 T-cells, ≥ 300/µL **And** Absent or low (up to 30% of normal) T-cell proliferation to antigens to which the patient has been exposed **Or** If the proliferation to antigen was not performed, but at least four of the following ten supportive criteria (at least one of which must be among those marked with an asterisk) below are present: ▪ hepatomegaly/ splenomegaly ▪ lymphadenopathy ▪ elevated IgE/ absolute eosinophil count ▪ *oligoclonal T-cells measured by CDR3 length or flow cytometry ▪ *>80% of CD3+ or CD4+ T-cells are CD45RO+ ▪ *proliferation to phytohaemagglutinin is reduced <30% of lower limit of normal ▪ *proliferative response in mixed leukocyte reaction is reduced <30% of lower limit of normal ▪ *mutation in SCID-causing gene.

Key: ESID – European Society for Immunodeficiencies, PCP – *Pneumocystis* pneumonia, CMV – cytomegalovirus, HIV – human immunodeficiency virus, IgE – immunoglobulin E
Sources: ESID,[21] and Primary Immune Deficiency Treatment Consortium.[39]

2.3.4 Treatment

A high-level schematic of the current treatment pathway for children with SCID in Ireland is presented in Figure 2.3.[32] The Department of Paediatric Infectious Diseases and Immunology, CHI at Crumlin, Dublin, currently acts as the national tertiary referral centre in the Republic of Ireland for children with suspected inborn errors of immunity.[6] Once a diagnosis of SCID is confirmed, the infant is kept as an inpatient in the local hospital until a bed is available at CHI Crumlin. Strict infection prevention and control (IPC) and isolation measures are put in place to reduce the likelihood of infection. The joint European Group for Blood and Marrow Transplantation (EBMT) and ESID treatment guidelines are followed.[40] Once the diagnosis of SCID has been established, HSCT from a matched sibling donor (MSD), or other matched family donors (MFD) is considered the gold standard, as explained below. With a limited number of exceptions in historical cases, the transplants take place at the Department of Paediatric Haematopoietic Stem Cell Therapy and Immunology at the Great North Children's Hospital in Newcastle upon Tyne, United Kingdom.

Figure 2.3 Treatment pathway for children with SCID in Ireland



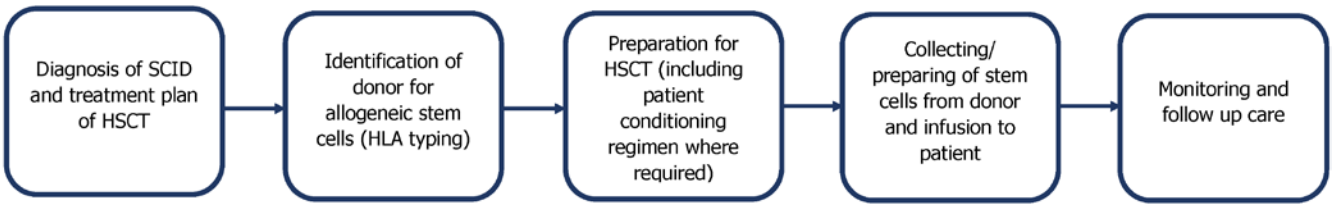
Key: ERT – enzyme replacement therapy; GOSH – Great Ormond Street Hospital; HLA – human leukocyte antigens; HSCT – haematopoietic stem cell transplantation; SCID – severe combined immunodeficiency.
Source: CHI Crumlin Consultant Paediatric Immunologist.[32]

Haematopoietic stem cell transplantation (HSCT)

Haematopoietic stem cells are immature cells which are found in the peripheral blood and in the bone marrow and which have the capacity to develop into different types of blood cells, including T-cells.[22] HSCT is a process by which haematopoietic stem cells are transplanted to the patient by infusion.[41] The transplanted cells then ideally develop into functional T-cells with the overall aim of HSCT being immune reconstitution (that is, the rebuilding of the immune system to be able to protect against infection).[41] It should be noted that while successful HSCT may resolve the immune deficiency associated with SCID, depending on the subtype there may be longer term sequelae arising from the genetic defect (for example, neurological impairments in ADA-SCID) which are not resolved by HSCT.[42]

Patients with SCID receive allogeneic HSCT, which involves the transplant of cells from a donor to the patient (recipient).[41] Donors are described in terms of how well 'matched' their cells are to that of the recipient; this is evaluated through HLA typing.[41] HLA describes markers which enable the body to differentiate between its own cells and foreign cells. Once a donor has been identified, stem cells are collected (known as harvesting) and prepared for infusion to the patient. Depending on the type of donor available and the SCID subtype, the child may require pre-transplant conditioning.[41] A simple schematic of the process of HSCT for children with SCID is outlined in Figure 2.4 below.

Figure 2.4 Schematic of HSCT process

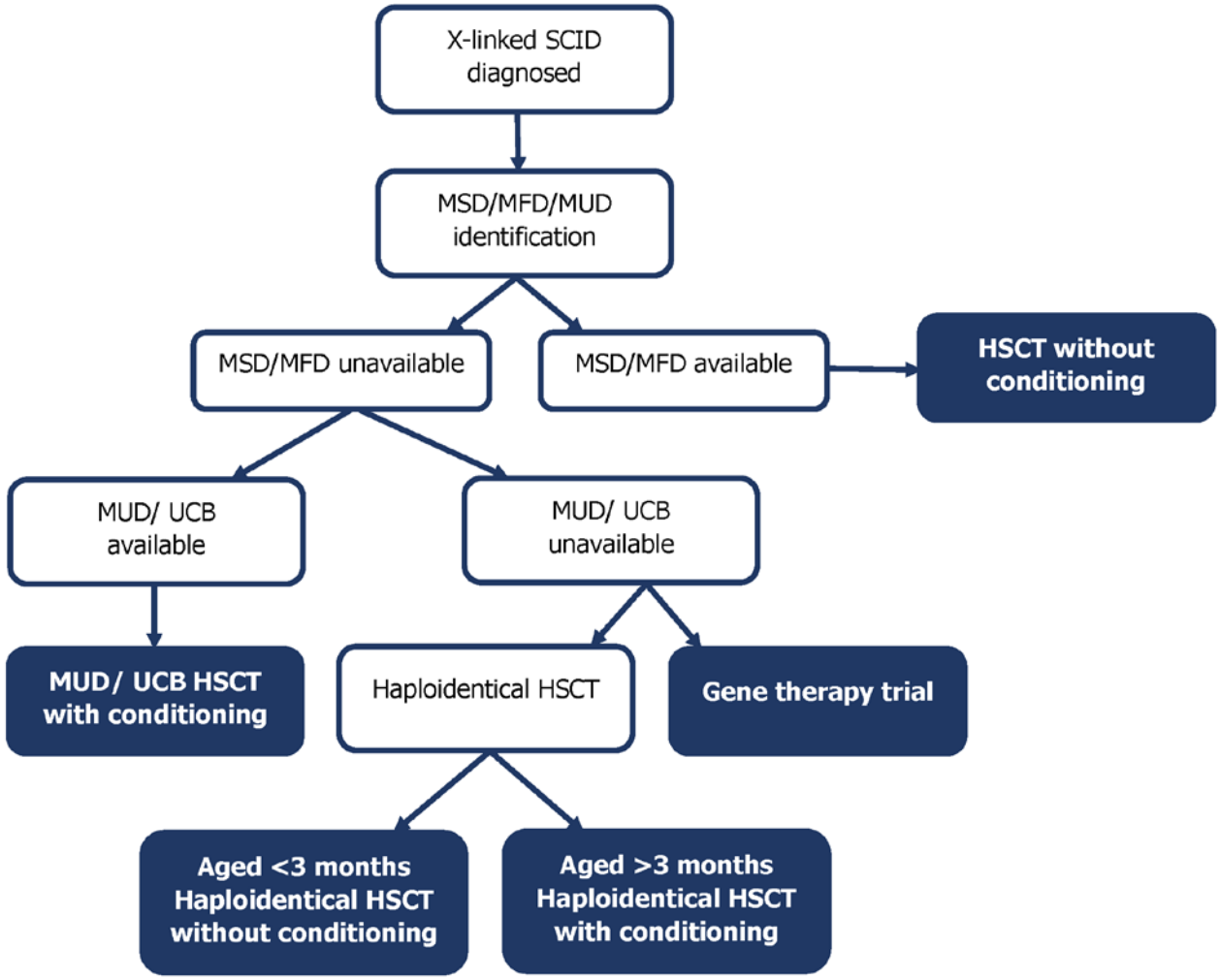


Key: HLA - human leukocyte antigen; HSCT – Haematopoietic stem cell transplantation; SCID – severe combined immunodeficiency.

As noted above, preferred donors for HSCT in patients with SCID are MSD or MFD, due to the lower risk of complications such as GvHD. In the absence of a MFD, the choice will depend on availability and suitability of a matched unrelated donor (MUD), or, in the context of clinical urgency, the consideration of a mismatched family donor (MMFD) or mismatched unrelated donor (MMUD). If there is a delay in donor identification, or an absence of matched donors, which is considered to be incompatible with the clinical status of the child, HSCT from a haploidentical family donor (that is a donor who is a half-match, such as a biological parent) or a mismatched unrelated cord blood donor will be the preferred choice. A sample

schematic for the treatment of X-linked SCID is provided in Figure 2.5 below, adapted from joint EBMT and ESID guidelines.[43]

Figure 2.5 Schematic of treatment for X-linked SCID



Key: HSCT – haematopoietic stem cell transplantation; MFD – matched family donor; MSD – matched sibling donor; MUD – matched unrelated donor; UCB – umbilical cord blood
Source: EBMT/ESID guidelines.[43]

Preparation for HSCT

In preparation for HSCT, any ongoing infections need to be treated, immunoglobulin replacement therapy and *Pneumocystis jirovecii* pneumonia prophylaxis need to be administered, and attention must be paid to nutritional status.[40] Patients should be isolated while preparing for HSCT with regular screening to allow timely treatment of infection. Live vaccinations should not be given. If the child has received the BCG vaccination prior to SCID diagnosis, intervention is needed to reduce the risk of complications from disseminated BCG infection (BCGosis).[40] If signs of infection are present, combination treatment (four drugs) with antimycobacterial drugs is

required. In the absence of symptoms, single-agent prophylaxis is recommended. If the mother of the infant is cytomegalovirus (CMV)-positive, then breastfeeding should cease to prevent possible infection with CMV through the breast milk.[40] Blood products require irradiation prior to administration in the case of transfusion. Where maternal T-cells are present, these need to be managed prior to HSCT through early serotherapy, immunosuppressive drugs, and immunosuppressive components in the conditioning regimen (see next section).[40]

While CHI at Crumlin manages the child before and after HSCT, currently, the procedures themselves (with a limited number of exceptions) take place in the United Kingdom for children with inborn errors of immunity as well as a number of other conditions.[44] To note, at the time of writing a HIQA assessment is ongoing in relation to the repatriation of paediatric HSCT services to Ireland, with a view to informing decision-making by the HSE.

Depending on home circumstances and the ability to adhere to IPC guidance, an infant may be kept as an inpatient or may return home while awaiting definitive treatment. If the infant is discharged home, ongoing IPC measures are required, including guidance relating to cleaning and laundry, feeding, hygiene, household visitors, and engaging in the community.[45] Once a suitable donor has been identified, the infant is transferred to the Department of Paediatric Haematopoietic Stem Cell Therapy and Immunology at the Great North Children's Hospital in Newcastle upon Tyne, United Kingdom.[6] If the child is medically well and on prophylaxis against infection, they may be transferred through standard commercial means (such as commercial flights or ferries); however, medically unstable infants may require chartered flight transfers. On admission, infants with SCID may undergo a variety of investigations including those outlined in Table 2.5 below.[46]

Table 2.5 Investigations that may be performed on admission to Great North Children's Hospital

Investigations for SCID patients*
Chest x-ray
Full blood count and differential
Biochemistry including renal, bone, liver, C-reactive protein and thyroid function
Blood culture for CMV, EBV, HHV6, and adenovirus
Microbiology for screening samples of urine, stool, nasopharyngeal aspirate and skin
Extended lymphocyte subsets (including naïve T-cells)
If residual T-cells present, TCR V-beta studies and αβ:γδ
Lymphocyte proliferations
Immunoglobulins including IgE
Foetomaternal engraftment analysis
Purine metabolites
Targeted genetic screen
Tissue typing

Key: CMV – cytomegalovirus, EBV - Epstein-Barr virus, HHV6 – Human Herpes virus 6, IgE – immunoglobin E, TCR – T cell receptor

*List is not exhaustive and specific investigations completed will depend on individual cases

Source: Great North Children's Hospital.[46]

Conditioning in HSCT

In advance of HSCT, a conditioning regimen may be required to prepare the patient's body to receive allogenic stem cells, and to reduce the likelihood of complications such as GvHD; however, such regimens are not always necessary when considering HSCT for SCID specifically.[41] Conditioning regimens typically involve the use of various chemotherapy agents (drugs) to suppress and reduce the number of existing immune cells. The necessity of conditioning, and the choice of regimen, depends on the donor type, phenotype, and, where identified, genotype of SCID, and whether maternal T-cells are identified (that is, maternal engraftment).[40]

Examples of conditioning regimens outlined by the EBMT/ESID guidelines are presented in Table 2.6. As there is limited experience in newborns regarding the drugs used in conditioning regimens, conditioned HSCT is not generally recommended before six to eight weeks of age.

Table 2.6 Conditioning regimen for SCID patients undergoing HSCT according to genotype (phenotype) and donor type

Genotype (phenotype)	Donor type	
	MSD / MFD	MUD / MMUD / MMFD
JAK3, IL2Rγ (T-B+NK-)	No conditioning/ C/D	C/D
RAG1/2, DCLRE1C (T-B-NK+)	C/D	C/D
IL7R, CD3 δ,ε,ζ, CD45 (T-B+NK+)	No conditioning/ C/D	C/D
ADA	No conditioning/ C/D	C/D
AK2	C/D	C/D

Key: MFD – matched family donor; MMFD – mismatched family donor; MMUD – mismatched unrelated donor; MSD – matched sibling donor; MUD – matched unrelated donor
Conditioning regimen C: Busulfan (AUC 60-70) days 5 to 2 prior to HSCT, Fludarabine (5-6×30 mg/m^2) days 7 to 2 prior to HSCT;
Conditioning regimen D: Treosulfan (3×10-14 g/m^2) days 5 to 3 prior to HSCT, Fludarabine (5×30 mg/m^2) days 6 to 2 prior to HSCT.
Source: EBMT/ESID inborn errors working party guidelines.[40]

Monitoring and follow-up care

Following HSCT, the child remains in Newcastle until such time as they are deemed medically fit to be discharged back to Ireland.[44] While the overall length of care fluctuates, the child will typically be in the United Kingdom for 4-6 months.

The length of hospital stay is variable and dependent on factors such as donor type, complications, requirements for stem cell boosts (see section 3.3.10), pre-transplantation status, and bed availability. The child will remain as an inpatient in the transplant unit until there is evidence of neutrophil engraftment, that red blood cell and platelet infusions are no longer required, and, where applicable, that any intravenous antibiotic therapy has completed. These criteria are generally reached at appropriately eight weeks post HSCT.[44] Intensive surveillance and monitoring is required with the child remaining on prophylaxis for the prevention of GvHD until T-cell engraftment occurs. This typically occurs at 3-4 months post HSCT; however, the timeframe is strongly dependent on host and donor factors. Surveillance and monitoring of the child post HSCT can occur as an outpatient, with the patient discharged to a step-down facility near the hospital. Investigations include weekly full blood counts, lymphocyte differentiation tests, liver function tests, and blood cultures and viral screens (to monitor for potential infection), with the infants closely monitored for signs of infection and GvHD.[44] Following engraftment, and in the absence of other complications, the child is discharged home and their medical care is transferred back to CHI Crumlin, who remain responsible for follow-up care.[44] Over time, the frequency of monitoring can eventually reduce, although all children require long-term surveillance for longer term complications such as development of autoimmunity.

Hypomorphic SCID and Omenn syndrome considerations

In the case of Omenn syndrome, immunosuppression (cyclosporine A or serotherapy with alemtuzumab) is frequently required before the patient undergoes HSCT. This is required to control skin and gastrointestinal infiltration and inflammation associated specifically with this inflammatory condition.(39) Conditioning prior to HSCT is also required in Omenn syndrome with similar regimens used as outlined in Table 2.6. HSCT in this patient cohort can be associated with a high rate of endothelial toxicities; to mitigate this, prophylaxis with the drug defibrotide can be considered.

Generally, patients with hypomorphic SCID presentations are clinically and immunologically heterogeneous. Clinical onset may be delayed and patients may present with autoimmunity and granuloma.(39) Similar conditioning regimens as those presented above are recommended prior to HSCT; however, the choice of regimen may be limited by the presence of comorbidities.

ADA-SCID specific considerations

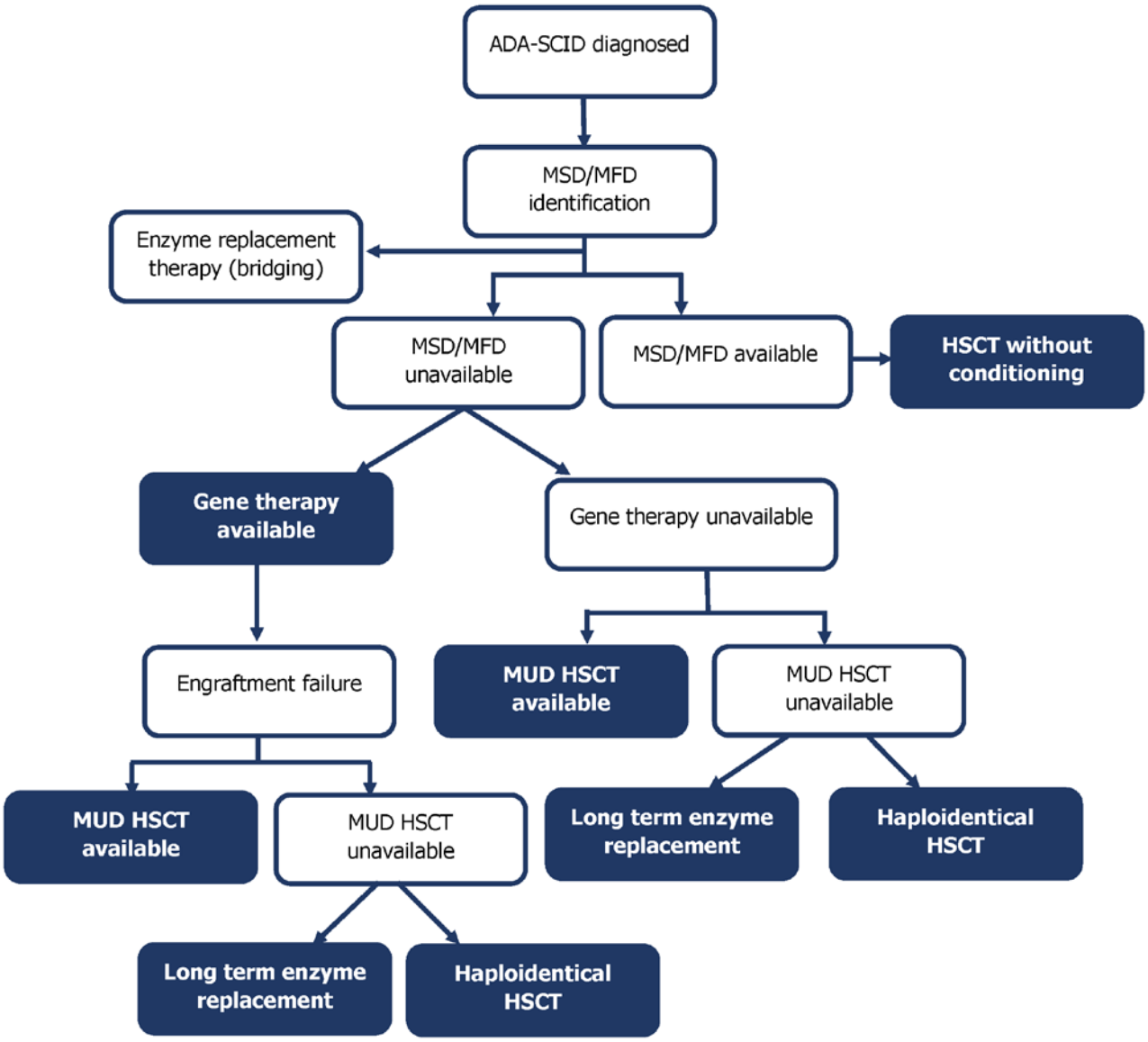
In the case of ADA-SCID specifically, while MSD/MFD HSCT remains the gold standard, additional treatment options are available and may be indicated where a matched sibling or family donor is not available (see Figure 2.5). The treatment options include gene therapy, and enzyme replacement therapy.(39, 47)

Gene therapy for ADA-SCID, which was first licensed by the European Medicines Agency (EMA) in 2016 (Strimvelis®, a gamma retroviral based treatment), involves performing a single infusion of autologous gene-corrected haematopoietic stem cells in order to insert a functional copy of the defective ADA gene.(47, 48) Gene therapy has been used to treat a limited number of Irish ADA-SCID patients within clinical trials of a lentiviral-based treatment at the Department of Paediatric Immunology and Gene Therapy in Great Ormond St. Hospital National Health Service (NHS) Trust, London.(6) However, outside of clinical trials, this type of treatment in Europe is currently only available in San Raffaele Hospital in Milan, Italy (Strimvelis®).(49) Where a matched sibling or family donor for HSCT is unavailable, and if gene therapy is not feasible or available, MUD or haploidentical HSCT should be considered.

Enzyme replacement therapy, with polyethylene-glycosylated ADA, is administered through weekly intramuscular injections. It is not recommended for long-term treatment and instead is largely considered to be a bridging therapy for the initial treatment of ADA-SCID while awaiting definitive treatment (that is, HSCT or gene therapy).

A sample schematic for the treatment of ADA-SCID, adapted from joint EBMT and ESID guidelines,[43] is provided in Figure 2.6 below.

Figure 2.6 Schematic of treatment for ADA-SCID



Key: HSCT – haematopoietic stem cell transplantation; MFD – matched family donor; MSD – matched sibling donor; MUD – matched unrelated donor
Source: EBMT/ESID guidelines.[43]

2.4 TREC-based screening for SCID

Newborn screening for SCID is possible through the quantification of TRECs,[7, 13] with this form of analysis being the generally accepted method of screening for SCID internationally.[5, 6, 13] The following describes the nature of the assay (section 2.4.1) and also outlines conditions, other than SCID, which result in TCL and may therefore be detected with the use of the TREC assay (section 2.4.2).

2.4.1 TREC assay

Background to assay

During normal thymic processes as described previously, TRECs are generated during TCR diversification and T-cell maturation.[13] As thymocytes become mature, the genes encoding TCR subunits undergo a process of DNA rearrangement.[13] TRECs are a DNA by-product of the recombination of the genes encoding the cell surface receptors for an antigen, and hence they are found in naïve T-cells that have left the thymus.[5, 13] TRECs are stable and maintained following cell division, but do not replicate and are consequently diluted out with cellular division. This means their measurement distinguishes between homeostatic expansion of T-cells in the periphery (that is, outside of the thymus) and the production of newly formed T-cells.[5, 13, 24] Therefore, the quantification of TRECs in an infant's blood provides a surrogate marker of thymic output of newly formed T-cells.[5, 24] An absence or depletion of TRECs is indicative of TCL.[5, 13]

The TREC assay is based on detection of one particular type of TREC known as δrec-ψJα and involves the use of the PCR.[13, 24, 25] As part of PCR, primers are used to amplify the coding joint of the δrec-ψJα TREC so that it may be detected. Using real-time quantitative PCR (qPCR), the TREC copy number may be readily determined, thus allowing for the quantification of TRECs.[13, 24] Specific kits that may be used to perform this assay are described below.

Originally developed to measure thymic output relating to aging processes and HIV infection, the TREC assay has since been modified for use in newborn screening.[5]

Use of the TREC assay in NBS; screening protocols and algorithms

The TREC assay is performed using DNA extracted from a sample (typically a 3.2 mm hole punch) of a collected DBS sample.[5] Appropriate cut-off values and algorithms are established and validated at the local level;[13, 24, 25] however, values of less than 25 TRECs/μl have been proposed within the literature as an optimal cut-off in terms of sensitivity and specificity for SCID and other TCLs.[50]

Screening protocols for SCID typically include the measurement of a control gene (beta-actin or RNaseP), in parallel to TREC quantification, as a test of DNA amplification.[13, 50] An abnormal TREC value typically results in retesting of the initial DBS, while failure of control gene DNA amplification typically leads to a request for a repeat DBS sample to be collected.[13, 50] An additional consideration in screening algorithms for SCID includes the categorisation and interpretation of results based on weeks of gestation. The inclusion of a component within a screening algorithm considering **prematurity** reflects the fact that preterm infants may typically present with low T-cell counts which begin to normalise with gestational age. Algorithms often include a different TREC cut-off for preterm infants and or use a repeated test at corrected gestational age.[50, 51] A sample screening algorithm presented for the EnLite™ Neonatal TREC Kit (see below) on submission for approval by the U.S. Food and Drug Administration (FDA) is presented in Figure 2.7.[52]

A previous systematic review of TREC-based screening for SCID completed in 2015 notes that TREC cut-off values, screening algorithms, handling of equivocal or inconclusive results, and subgroup treatment vary among different screening sites that have implemented TREC-based screening.[50] Importantly, as the quantification of TRECs indicates TCL, the test is not necessarily specific to SCID and hence there is a **requirement for follow-up immunological confirmatory testing** as per the diagnostic guidelines outlined.[25, 50]

A number of sites internationally have further been noted to include the use of a kappa-deleting recombination excision circles **(KREC) assay** in tandem with the TREC assay. The quantification of KRECs is used to identify infants that may have significant B-cell lymphopenia (BCL), such as those with X-linked agammaglobulinemia. There is also some limited evidence to suggest that tandem KREC-based testing may have added benefit in the detection of delayed- or late-onset ADA-SCID specifically.[50, 53, 54] However, it is noteworthy that within the newborn bloodspot programme in Sweden, while TRECs and KRECs are measured in tandem, the KREC value is not considered in isolation for onward referral (that is, the infant must have evidence of TCL with or without BCL).[55]

Technology used in TREC and KREC assays (test kits)

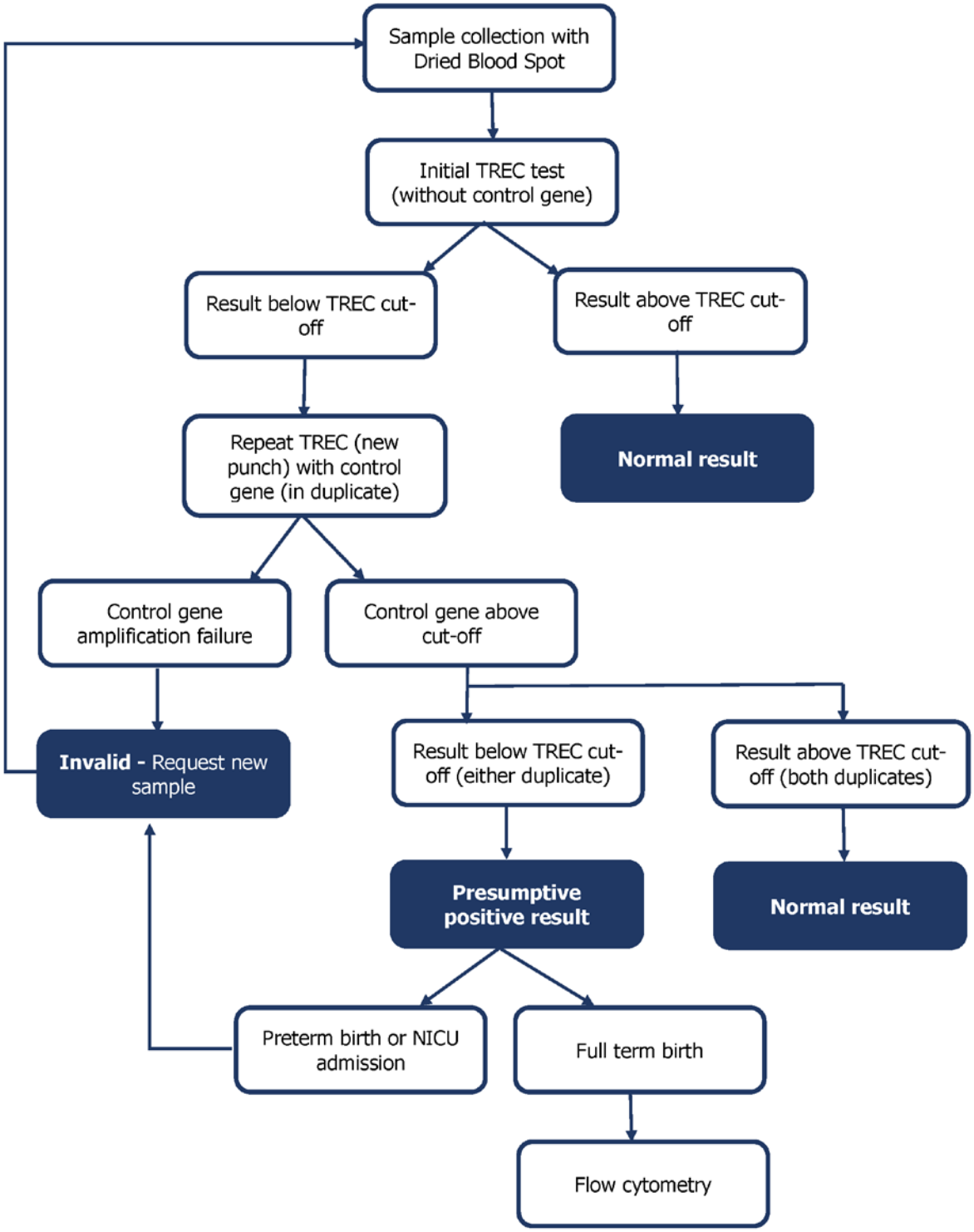
Commercially available kits to perform the TREC assay are now available for use alongside existing PCR equipment.[13] Up to the time of writing, at least two commercially available kits have been described, namely: the **Perkin Elmer EnLite Neonatal kit ™** and the **Immuno IVD SPOT-it™ screening kit** (formerly, the SCREEN-ID neonatal screening kit).[56, 57] The EnLite kit received FDA approval for marketing in 2014, and has CE-marking (that is, that a product meets requirements for sale in the EEA).[52, 56] The SPOT-it kit became available after the EnLite

authorisation, though the precise year of this entry to the market is unclear.[58] As with the EnLite kit, the SPOT-it kit is CE marked.[57] Notably, with regard to the KREC assay, the SPOT-it screening kit is equipped for both TREC and KREC quantification.[57]

Regulation of test kits

It should be noted that *in vitro* diagnostic medical devices (IVDs) which are intended to quantify TRECs or KRECs for the purpose of screening newborns for SCID are subject to EU IVD Regulation 2017/746. This new EU Regulation has applied since 26 May 2022 and strengthens the oversight of IVDs. While self-certification of these devices was previously permitted under the IVD Directive 98/79/EC, the conformity assessment for CE-marking of these devices under the new Regulation (Class C) will now require involvement of a Notified Body to ensure their safety and performance. These devices are classified under rule 3(m) based on their intended purpose: '*for screening for congenital disorders in new-born babies where failure to detect and treat such disorders could lead to life-threatening situations or severe disabilities'*.[59]

Figure 2.7 Testing Algorithm for EnLite™ Neonatal TREC Kit (adapted from submission during FDA approval process)



Source: FDA approval document in response to marketing authorisation application for the EnLite™ kit.[52]

2.4.2 Non-SCID TCL causes

As mentioned, there are a range of causes of TCL that may be detected by TREC analysis. Non-SCID related congenital conditions that may present with abnormal TREC values include:[25, 60, 61]

- 22q11.2 Deletion Syndrome (DiGeorge syndrome)
- combined immunodeficiency
- ataxia telangiectasia
- DOCK 8 deficiency
- Anhidrotic ectodermal dysplasia with immune deficiency
- Trisomy 21
- Trisomy 18
- Kabuki syndrome
- CHARGE syndrome
- Noonan syndrome
- Jacobsen syndrome
- Fryns syndrome
- CLOVES syndrome
- Renpenning syndrome
- TAR syndrome
- VACTERL syndrome
- Dandy Walker syndrome
- Barth syndrome
- Schimke immuno-osseous dysplasia
- cartilage hair hypoplasia
- cytogenetic abnormalities.

Furthermore, low TREC values can result from secondary causes such as:[25, 60, 61]

- prematurity (typically TCL in those born before 37 gestational weeks which progressively normalises over time)
- congenital heart disease
- chylothorax
- gastrointestinal anomalies
- vascular leakage
- hydrops

- neonatal leukaemia
- maternal causes (such as autoimmune disease, HIV infection, and immunosuppression).

Pathways for non-SCID TCL

The above conditions represent differential diagnoses that may occur during screening for SCID. Given that a number of these conditions are considered to be clinically significant and associated with persistent TCL, it has been highlighted that it is important to consider the infrastructure for diagnosis, follow-up and management for such diagnoses within decision-making on screening for SCID.[50, 62] Two publications from the United States (2019 and 2021) have highlighted that there are currently no established consensus guidelines or algorithms for non-SCID TCL cases detected through screening programmes for SCID.[63, 64] Similarly, from the international sources described in section 2.5 below, no clinical pathways or guidelines were identified.

As will be discussed in chapter three and four, the incidence of non-SCID TCLs detected through NBS programmes is likely higher than that of SCID, which has been highlighted as a potential burden for these programmes.[63] The detection level of non-SCID TCLs for a given screening programme will vary depending on the TREC cut-off, screening algorithm, and diagnostic criteria in use.[50] As there are many causes of non-SCID TCL, including congenital syndromes, secondary causes of TCL, idiopathic TCL and transient instances of TCL (such as with preterm infants), decisions surrounding the management of these non-SCID TCL cases are often made on a case-by-case basis and specific testing depends on clinical evaluation of any comorbidities.[63]

Given the number of potential secondary causes and congenital syndromes that may be detected through newborn screening for SCID, it is beyond the scope of this assessment to examine each in detail. For illustrative purposes, a vignette focusing on 22q.11.2 Deletion Syndrome, also known as DiGeorge syndrome, is presented in Appendix 2.3; this syndrome was frequently noted as a differential diagnosis in the studies outlined in chapter four of this report.

2.5 International practice in newborn screening for SCID

To provide an overview of current international practice regarding newborn screening for SCID, a scoping search was performed which examined 34 countries deemed to be of most relevance to Ireland, including those in the European Economic Area, the United Kingdom, the United States, Canada, Australia and New Zealand (see Appendix 2.4). A targeted grey literature search (for example, national

public health organisations, and the websites of governmental departments and relevant agencies), supplemented with the findings of a recent HIQA publication,[17] and peer-reviewed literature where necessary,[65-67] was performed. Thirty-four countries were assessed, with a number including specific territories or regions (for example, Canada).

A summary of the findings of this review is presented in Table 2.7, followed by detailed findings for each specific country. As outlined in Table 2.7, of the 34 countries that were examined, newborn screening for SCID was fully implemented in nine countries, regionally implemented in three countries, under implementation in one country, under review and or being piloted in four countries, and in one country, had received a conditional recommendation for implementation following a HTA and a pilot. For countries presenting sufficient information, the majority of newborn screening for SCID was noted to be TREC-based, with four countries further using combined TREC- and KREC-based screening.

Table 2.7 Overview of countries identified as having NBS screening for SCID in place, undergoing implementation, undergoing pilot, and under review

Country/Provence	Level of implementation
Australia	Under review for all territories; Pilot in New South Wales; Queensland and Victoria have committed to implementation in 2023.
Austria	Under evaluation as of 2021
Canada	Regional implementation
Alberta	Full implementation as of 2019
Manitoba	Under implementation as of 2021
New Brunswick Nova Scotia Prince Edward Island	Full implementation as of 2016
Ontario	Full implementation as of 2013
Quebec	Evaluation completed in 2022 with positive recommendation
Saskatchewan	Recommended for screening in 2022
Denmark	National implementation as of 2020
Finland	Recommended for screening in 2020
France	HTA completed in 2022 with conditional recommendation
Germany	National implementation as of 2019
Iceland	National implementation as of 2017
Italy	Regional implementation and pilot
The Netherlands	National implementation as of 2021
New Zealand	National implementation as of 2017
Norway	National implementation as of 2018
Poland	Pilot
Slovakia	Pilot
Spain	Regional implementation as of 2017
Sweden	National implementation as of 2019
Switzerland	National implementation as of 2019
United Kingdom	Under review and ongoing pilot
United States	Addition to recommended panel in 2010; As of 2021, implemented in all 50 states and Puerto Rico.

Australia

Following recommendation in 2018, and after completion of an initial review, the Australian Standing Committee on Screening agreed that a full review of newborn screening for SCID was warranted for all territories.[68] The full review is currently underway.[68] Screening for SCID is under pilot in New South Wales.[69] Queensland and Victoria have committed to the implementation of SCID screening in 2023.[70]

Austria

A 2022 press release by the Medical University of Vienna indicated that screening for SCID has been included in the Austrian newborn screening programme as part of a research project which started in 2021.[71]

Canada

In Canada, newborn screening follows provincial mandates so the conditions included in newborn screening programmes can vary across provinces. Six of the ten Canadian provinces currently screen for SCID, with Ontario being the first province to adopt screening for SCID in 2013.[72] The Maritime Newborn Screening Programme was created in 2014 and is responsible for newborn screening for the provinces of New Brunswick, Nova Scotia and Prince Edward Island, with screening for SCID introduced in 2016.[73] In Alberta, the Newborn Metabolic Screening Program is delivered by Alberta Health Services and commenced screening for SCID in 2019.[17] Screening for SCID as part of the Manitoba Newborn Screening Program commenced in 2021.[74] Each of the six provinces were noted to screen for SCID by TREC assay; however, the provinces of Manitoba and Ontario also employ targeted mutation screening for ZAP70 and IKBKB deficiencies, which are prevalent in these regions.[72, 75] In 2022, the Saskatchewan health minister announced that the province will expand its newborn screening programme to include several new conditions, including SCID.[76] The addition of SCID to the Quebec NBS programme was evaluated by the Institut National d'Excellence en Santé et en Services Sociaux (INESSS) and a positive recommendation was published in May 2022.[77] A number of considerations were outlined alongside the recommendation to add SCID to the NBS programme, including the need for:

- the facility overseeing the screening to establish performance standards for the test and a population-specific TREC cut-off value to limit the identification of non-SCID TCLs.
- guidance for the disclosure of incurable incidental findings that may be identified by this screening, such as ataxia-telangiectasia.

- the development of a specific algorithm for premature newborns and those admitted to neonatal intensive care units (who should be screened prior to discharge).
- the administration of the BCG vaccine to be postponed until screening results are obtained for newborns in the Nunavik community (who are known to be at an increased risk of SCID).
- the dissemination of information about SCID and the screening test in order to alleviate concerns about screening in the general population and, in particular, among future parents.

Denmark

In Denmark, the Statens Serum Institut is responsible for the national screening programme and receives its mandate from the Ministry of Health. While the programme is implemented at a regional level, no regional variation in the conditions included for newborn screening has been noted.[17] Screening for SCID by TREC assay has been included in the newborn screening panel since 2020.[78]

Finland

In Finland, each municipality or hospital district is responsible for providing screening programmes and can decide which conditions to include in their screening panel, resulting in variation in the conditions screened across Finland.[79] The Congenital Metabolic Screening Centre in the South West Hospital District of Finland includes SCID in its newborn bloodspot screening panel.[80] In addition, in September 2020 the Finnish Healthcare Services Selection Council published its recommendation supporting the addition of SCID screening by TREC assay to newborn bloodspot programmes in Finland.[81]

France

The Haute Autorité Santé (HAS) published an *a priori* evaluation for the addition of SCID to the French newborn screening programme in February 2022.[82] The publication recommends the addition of SCID to the programme, though this is to be on a conditional basis. These conditions include:

- The implementation of screening for SCID is subject to a mandatory five-year evaluation, and regular intermediate evaluations.
- Screening for SCID can only be implemented, even in conditional form, if the stages leading to HSCT can be carried out within two months from birth.

- There is harmonisation of pathways across the country to avoid territorial inequalities.

Germany

The German newborn bloodspot screening programme is regulated nationally by the Federal Joint Committee of Doctors and Health Insurance Funds (G-BA). Following approval by the G-BA in 2019, testing for newborn screening for SCID by TREC assay was added to the national screening programme.[17, 83]

Iceland

In 2016, the Medical Director of Health agreed to screen all newborns in Iceland for SCID. The screening was set up at Landspítali's Department of Immunology in May 2017.[84] TREC- and KREC-based screening is noted to be in use.

Italy

Screening for SCID using TREC analysis, and ADA-SCID using MS/MS technology, was implemented in Tuscany, Italy, in 2017.[31, 85] Pilot TREC-based screening for SCID is being undertaken in the Liguria region.

The Netherlands

The Dutch Ministry of Health adopted the advice of the Dutch Health Council to include SCID in the Dutch newborn screening programme in 2015.[86] Following a pilot programme, screening for SCID was implemented nationally in 2021.[87]

New Zealand

In 2014, following a literature review and a cost-effectiveness analysis, the New Zealand Screening body made a positive recommendation for the inclusion of SCID to newborn screening. Newborn screening for SCID was formally introduced in New Zealand in 2017.[88]

Norway

After evaluation by the National Institute of Public Health, it was determined that the newborn screening programme could be extended to include screening for SCID and other severe TCLs. Screening for SCID was officially added to the programme in January 2018.[89]

Poland

A 2021 publication reported results from a survey on neonatal screening for 51 European countries, with data collected up to 2020.[66] According to the response to this survey, screening for SCID is under pilot in Poland.

Slovakia

According to the Newborn Screening Center of Slovakia at the Banska Bystrica Children's University Hospital, expanded screening for congenital and inherited diseases in newborns was introduced in 2013 but did not include screening for SCID.[90] According to the response to the above survey, screening for SCID is under pilot in Slovakia.[66]

Spain

In September 2016, the Department of Public Health of the Catalonian Government officially communicated the approval of SCID in its NBS programme. In January 2017, newborn screening for SCID in Catalonia was implemented (beginning as a six month pilot prospective pilot study) and has been in place in the region since.[91] In addition, since 2019, ADA-SCID screening by tandem mass spectrometry has been implemented in the region to mitigate the potential for missed cases by TREC-based screening.[91]

Sweden

In Sweden, a regional pilot study was carried out between 2013 and 2016. Children were referred for further examination based on low TRECs and or low KRECs. The study resulted in a positive decision from the screening council at the Swedish Board of Health and Welfare with newborn screening for SCID introduced at the national level in 2019, subsequent to a change in the Swedish biobank law.[55] However, while TRECs and KRECs are measured in tandem, there is no onward referral solely on the basis of an abnormal KREC value (that is, the infant must have evidence of TCL with or without BCL).[55]

Switzerland

In Switzerland, decision-making with respect to newborn screening is devolved to the 26 individual cantons, with national recommendations made by expert committees on screening programmes. Screening for SCID began in 2019 with TREC- and KREC-based analysis.[92]

United Kingdom

The addition of SCID to the United Kingdom NBS programme was assessed by the UK National Screening Committee (NSC) in 2017.[62] At that time, a decision was

made to not recommend screening for SCID. Considerations for this decision included the potential false positives associated with screening, the concerns regarding the management and outcomes of infants with TCLs caused by other conditions, the number of infants already identified on the basis of family history (and thus, the reduced added value of screening), and the capacity of laboratories. However, it was recommended that a pilot evaluation of TREC-based screening for SCID be undertaken by the NHS to inform a subsequent review by the UK NSC.[58] This evaluation began on the 6 September 2021 with select hospitals in England taking part; a detailed overview of the planned methodology and stakeholder groups involved has been published, including a detailed screening algorithm with provision for both full term and preterm infants.[58] The evaluation aims to screen two thirds of babies born in England over a two-year period. As part of this evaluation, the outcomes and costs of care for infants identified with SCID through screening will be compared to those identified across the rest of the United Kingdom in the absence of screening. The evaluation will further assess the impact of screening on the family; carers of children who had true negative, false positive, and true positive screening outcomes will be included, along with the carers of children who were identified as having SCID, and other conditions, without screening.[58] The evaluation is expected to last for two years prior to revisiting the original recommendation made.[58, 93]

United States

In the United States, while individual states decide which disorders are included in their individual screening programmes, the Advisory Committee on Heritable Disorders in Newborns and Children recommends that states test for a core panel of 31 congenital disorders.[94] SCID was added to the core Recommended Uniform Screening Panel in 2010, and as of 2021, all 50 states, and Puerto Rico, currently screen for SCID.[13, 95] Owing to the potential for missed cases of delayed-onset ADA-SCID, as of 2019, the state of Michigan has implemented screening for ADA-SCID by tandem mass spectrometry in addition to TREC-based screening.[95]

2.6 Discussion

The purpose of this chapter was to describe the key elements of the technology under consideration. It is important to emphasise that while screening for SCID is facilitated through the quantification of TRECs (the TREC assay), the technology under consideration is considered to be the programme of screening for SCID as a whole, rather than the isolated screening test. As such, for a change to the screening programme to be implemented, each individual element of the screening pathway will require consideration; these include the target population, the burden of the disease, the provision of patient information and obtaining of informed consent (in particular, the understanding of the purpose and intent of screening

compared to diagnostic testing), the accuracy of the test, and pathways of referral, diagnosis, treatment and follow-up. As this proposed form of screening would represent an addition to an existing screening programme in Ireland (that is, the NNBSP), careful consideration of the impact and changes required will be needed to ensure confidence in the existing programme is maintained.

The NNBSP in Ireland currently screens for nine conditions, including the recent addition of ADA-SCID.[18] As ADA-SCID may be detected through the measurement of metabolites (adenosine and deoxyadenosine), it may be screened for via MS/MS, an existing laboratory platform used by the NNBSP; this platform cannot be used to screen for the remaining forms of SCID. It is noted that a proportion of children with SCID are also identified through risk-based detection at birth. While it is anticipated that TREC-based screening would identify all SCID subtypes including ADA-SCID, it is important to consider what it may offer over and above that which is captured in the current programme and through risk-based detection. This detail will be explored within the epidemiology section in chapter three of this report.

As there is an accepted treatment for SCID, it is likely that the benefits of screening will be most impactful for those who are diagnosed clinically and hence may receive treatment earlier. The potential size of this population and the burden of the disease associated will be explored in chapter three of this report. The potential benefit of early versus later treatment will be detailed in chapter five.

Newborn screening for SCID is possible through the quantification of TRECs,[7, 13] with this form of analysis being the generally accepted method of screening for SCID internationally.[5, 6, 13] However, TREC-based screening is not specific to SCID, that is, it also identifies other TCL. These TCL, some of which may be clinically significant are due to a diverse range of congenital and secondary causes. The accuracy, logistical, and resource implications of TREC-based screening, in terms of the detection of both SCID and non-SCID TCLs, are important considerations which will be explored in subsequent chapters of this report.

Newborn screening for SCID was noted to be fully implemented across a number of countries in Europe, alongside New Zealand and the United States. It was also noted to be undergoing regional implementation, ongoing implementation, piloting and current review in a number of countries included in the international review. Three screening programmes (Tuscany, Michigan and Catalonia), were noted to screen for both ADA-SCID (using tandem mass spectrometry) and all SCID subtypes (using TREC-based screening). The reported rationale for this approach was the potential for TREC-based screening to miss cases of delayed onset ADA-SCID. While the majority of newborn screening programmes for SCID were noted to be TREC-based, four countries have further implemented combined TREC- and KREC-based

screening. Given the implementation of such screening programmes, several studies have been published which detail population-based screening programmes internationally, including TREC cut-offs and algorithms used. These will be detailed in chapter four of this report.

Collectively, the technology under consideration within this HTA, that is newborn screening for SCID, appears to be associated with an established means of screening in terms of a clinical test and a defined clinical pathway in terms of diagnosis and treatment, and has been implemented across many countries globally. SCID represents a rare, but serious, condition in terms of overall outcomes. Challenges are posed by the potential for incidental findings occurring as part of a screening programme for SCID, including the need for appropriate clinical pathways to be in place to manage such diagnoses. The following chapters will focus on detailed examinations of the epidemiology and burden of disease associated with SCID, the accuracy of TREC-based newborn screening for SCID, the benefit of early versus late intervention for children diagnosed with SCID, the cost-effectiveness and resource implications of screening, and organisational, ethical and or social considerations relevant to screening for SCID.

3. Epidemiology

Key points

- Severe combined immunodeficiency (SCID) results from mutations in at least 19 known genes, and thus a large number of subtypes of SCID exist. The condition is typically associated with T-cell lymphopenia; however, depending on the gene affected, SCID may be further associated with impairment of B-cell and natural killer cells, giving rise to a variety of immunophenotypes.
    - Hypomorphic mutations in SCID genes (mutations which result in reduced levels of activity of the gene product) result in particular forms of SCID known as **atypical SCID** and **Omenn syndrome**.
- The majority of the subtypes of SCID are inherited in an **autosomal recessive** manner; however, the proportions of individual subtypes vary internationally.
    - **ADA-SCID** has a particularly high incidence in Ireland as a proportion of all SCID cases, making up approximately 50% (n = 14) of cases diagnosed between 2005 and 2020. Of the 14 ADA-SCID cases documented, 13 were noted to be of Irish Traveller ethnicity.
    - This high incidence of ADA-SCID has been attributed to a founder mutation of the ADA gene (homozygous c.646G > A mutation in exon 7).
- **X-linked SCID** is a form of SCID which has an X-linked recessive pattern of inheritance, and therefore retains a relatively constant global incidence. This form of SCID arises from mutations in the IL2RG gene on the X-chromosome.
- Cases of SCID are typically asymptomatic at birth. Without newborn bloodspot screening (NBS) screening, identification relies on **risk-based detection at birth** or **clinical presentation**. Clinical presentation of SCID typically manifests (usually in the first three of six months of life) as recurrent and often severe infections, often with non-infectious complications such as a failure to thrive. ADA-SCID is additionally characterised by marked neurological and physiological abnormalities, while Omenn syndrome involves desquamating erythroderma.
    - Children with SCID are further vulnerable to vaccine-specific infection from receiving live vaccines. Nine such instances were documented in the Irish group.

- **Between 2005 and 2020, there were 27 children diagnosed with SCID in Ireland.** Within this 15 year time period, there were 1,073,519 births registered, reflecting a birth prevalence of **1 in 39,760 births**. This may reflect an underestimate given international evidence that, without screening, a proportion of infants may not survive to formal diagnosis.
    - Of the 27 documented cases in Ireland, eight infants were diagnosed through risk-based detection at birth (that is, through family history or by virtue of Irish Traveller ethnicity) and 19 were diagnosed clinically (that is, through symptomatic presentation). Excluding ADA-SCID cases, three infants were diagnosed at birth and 10 clinically.
- Consistently, data suggest that the age at which children are diagnosed, and, consequently, the age at which they undergo definitive treatment, is lower for those identified on the basis of screening or family history compared with those diagnosed clinically. Considering data from Irish cases:
    - Of those children diagnosed clinically, the median **age at symptom onset** was 33 days and the median age at clinical presentation was 77 days.
    - The median **age of diagnosis** was as follows:
        - Diagnosis through risk-based detection at birth: 0 days (range 0 to 14)
        - Diagnosis occurring clinically: 98 days (range 20 to 229).
    - The median **age at definitive treatment** was as follows:
        - Diagnosis through risk-based detection at birth: 54 days (range 24 to 258)
        - Diagnosis occurring clinically: 184 days (range 67 to 354).
- At the national and international level, there is evidence to suggest that the **number of infections** prior to diagnosis, prior to treatment, and active at the time of treatment tends to be **higher in those diagnosed clinically** compared with those identified on the basis of screening or family history.
- The morbidity and mortality associated with SCID is considerable; however, such factors appear largely reliant on the presence or absence of infections and complications prior to definitive treatment. While age is frequently cited as a

significant factor in the success of treatment, it appears that this serves largely as a proxy for the clinical condition of the child prior to treatment.

- From 27 cases of SCID in Ireland, 25 (92.6%) survived to definitive treatment, while two deaths occurred prior to treatment; both of these were in the group (n= 19) diagnosed clinically. Of these 25 children, **24 were alive at 24 months follow-up;** one infant, who had been diagnosed clinically, died soon after transplant.

The purpose of this chapter is to describe the epidemiology of SCID, including the aetiology, incidence, clinical presentation, and burden of the disease. International data and data from 27 children diagnosed with SCID in Ireland between 2005 and 2020 are included where relevant.[96] The Irish data were obtained from the Department of Paediatric Infectious Diseases and Immunology, Children's Health Ireland (CHI) at Crumlin, Dublin, and are further segregated into all SCID cases and SCID cases excluding ADA-SCID diagnoses.

3.1 Aetiology

3.1.1 Genotypes and phenotypes

While SCID is typically characterised by T-cell lymphopenia (TCL), B-cells may also be directly affected or impacted, in terms of activation, by an absence of CD4+ helper T-cells.[25] The collective pathophysiology of SCID typically affects both cell-mediated and humoral immunity,[2] with impaired development, differentiation, or activation of T-cell and B-cells at various points of the immune pathway, depending on the gene affected.[22, 25] As outlined in Figure 3.1, SCID results from mutations in at least 19 known genes. These mutations give rise to a large number of subtypes, which are typically named in terms of a deficiency of the gene product that is impacted (Table 3.1).[2, 21] Of note, a number of classification systems exist for SCID, including those presented by the International Union of Immunological Societies (IUIS) and European Society for Immunodeficiencies (ESID).[2, 21] The classifications used, as presented in Figure 3.1, represent a simplification of phenotypes for the purposes of illustration.[2, 3]

Substantial phenotypic and clinical heterogeneity exists within SCID; this is also the case within groups of patients with mutations in the same gene and even between individuals with near identical gene mutations.[2, 3]

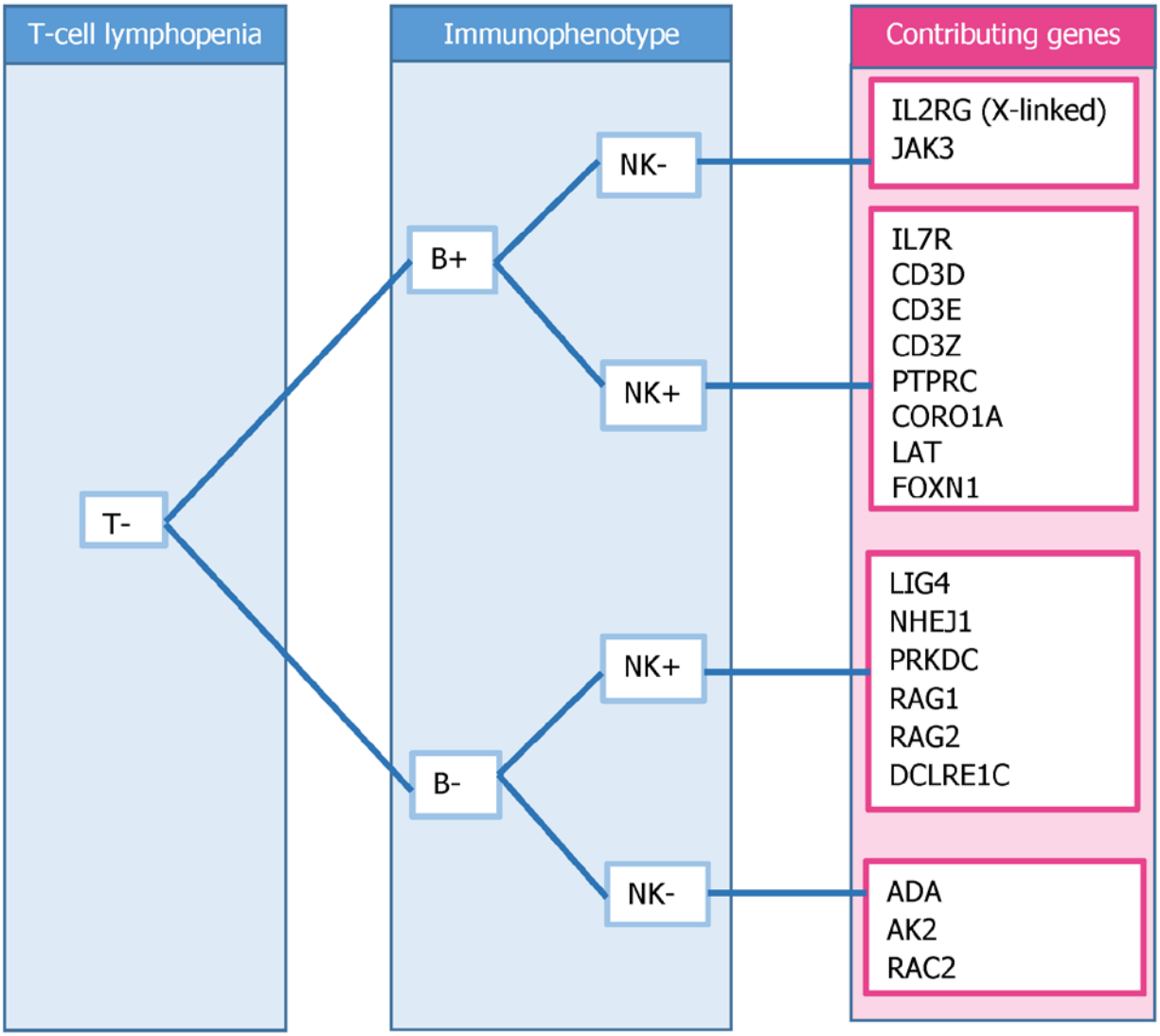
As shown in Figure 3.2, amorphic mutations (that is, a loss of gene function) result in typical SCID whereas hypomorphic mutations (that is, when a gene product exhibits reduced rather than absent activity) in several of the genes that cause SCID

may result in Omenn syndrome, or in atypical SCID (also known as "leaky" SCID).[2] In the case of atypical SCID, mutations may involve the RAG1, ADA, and IL2RG genes and can present with less severe impairment of T-cells overall than in typical SCID.[21] In Omenn syndrome, mutations of DCLRE1C, RAG1, RAG2, CARD11, LIG4, and IL7Rα have been documented.[21] Variant SCID typically refers to infants presenting with signs and symptoms of SCID, but without mutations in known SCID-causing genes.[7]

Fischer et al.[25] highlight how various genes associated with SCID impact on the development, differentiation or activation of T-cell and B-cells:

- precursor cells may be impacted by AK2 and ADA mutations
- defective common γ-chain-dependent cytokine signalling arise through IL2RG, IL7Rα and JAK3 mutations
- failure of T-cell receptors (TCR) and B-cell receptors (BCR) rearrangements result from mutations in RAG1, RAG2, DCLRE1C, PRKDC, LIG4 and NHEJ1
- defective pre-TCR and TCR signalling arise from mutations in CD45, CD3D, CD3E and CD3Z.

Figure 3.1 Classification of SCID; adapted from ESID and IUIS.



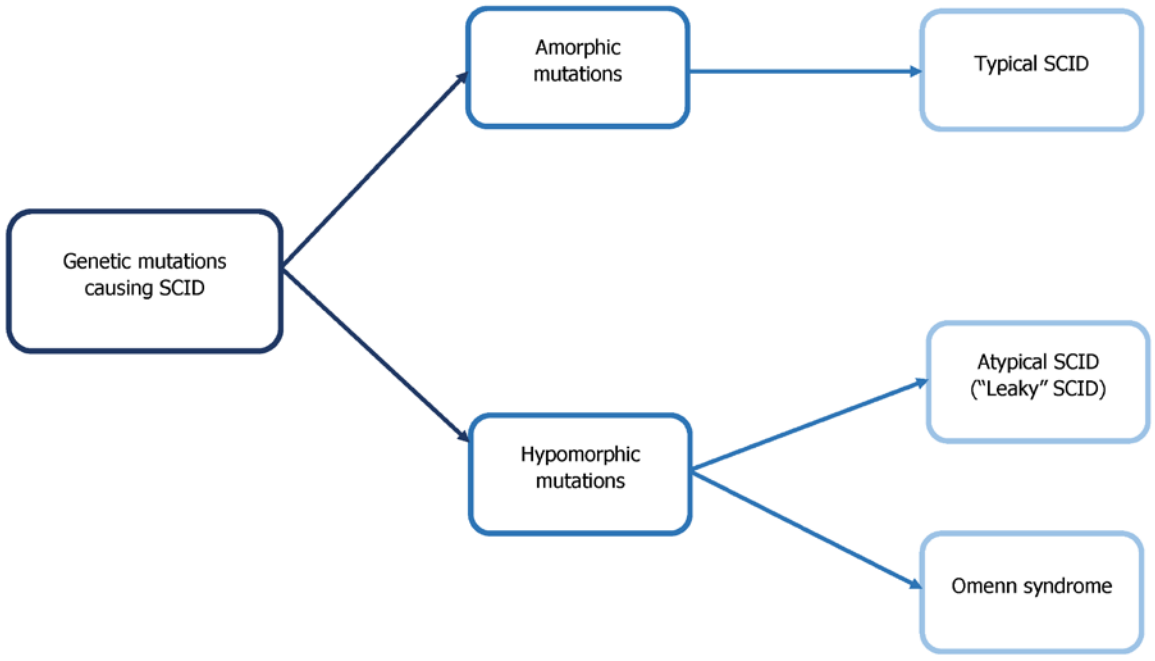
Sources: Human inborn errors of immunity: 2019 update on the classification from the International Union of Immunological Societies Expert Committee,[2, 3] and European Society for Immunodeficiencies working definitions for clinical diagnosis of PID.[21]

Table 3.1 SCID subtypes and associated genes; adapted from IUIS

SCID subtype	Gene
γc deficiency (X-Linked)	Interleukin 2 receptor gamma chain (IL2RG)
Janus Kinase 3 (JAK3) deficiency	JAK3
Interleukin 7 Receptor alpha (IL7Rα) deficiency	IL7Rα
CD45 deficiency	Protein Tyrosine Phosphatase Receptor Type C (PTPRC)
CD3δ deficiency	CD3δ
CD3ε deficiency	CD3ε
CD3Z deficiency	CD3Z
Coronin-1A deficiency	CORO1A
Linker for activation of T cells (LAT) deficiency	LAT
Recombination-activating gene (RAG) deficiency	RAG1/ RAG2
Artemis deficiency	DNA Cross-Link Repair 1C (DCLRE1C)
DNA PKcs deficiency	Protein Kinase, DNA-Activated, Catalytic Subunit (PRKDC)
Cernunnos/XLF deficiency	Non-Homologous End Joining Factor 1 (NHEJ1)
DNA ligase IV deficiency	LIG4
ADA deficiency (ADA-SCID)	ADA
Adenylate kinase 2 (AK2) deficiency (Reticular Dysgenesis)	AK2
Activated RAC2 defect	RAC2
Winged Helix Deficiency	Forkhead Box N1 (FOXN1)

Source: International Union of Immunological Societies Expert Committee.[2, 3]

Figure 3.2 Genetic mutations and types of SCID



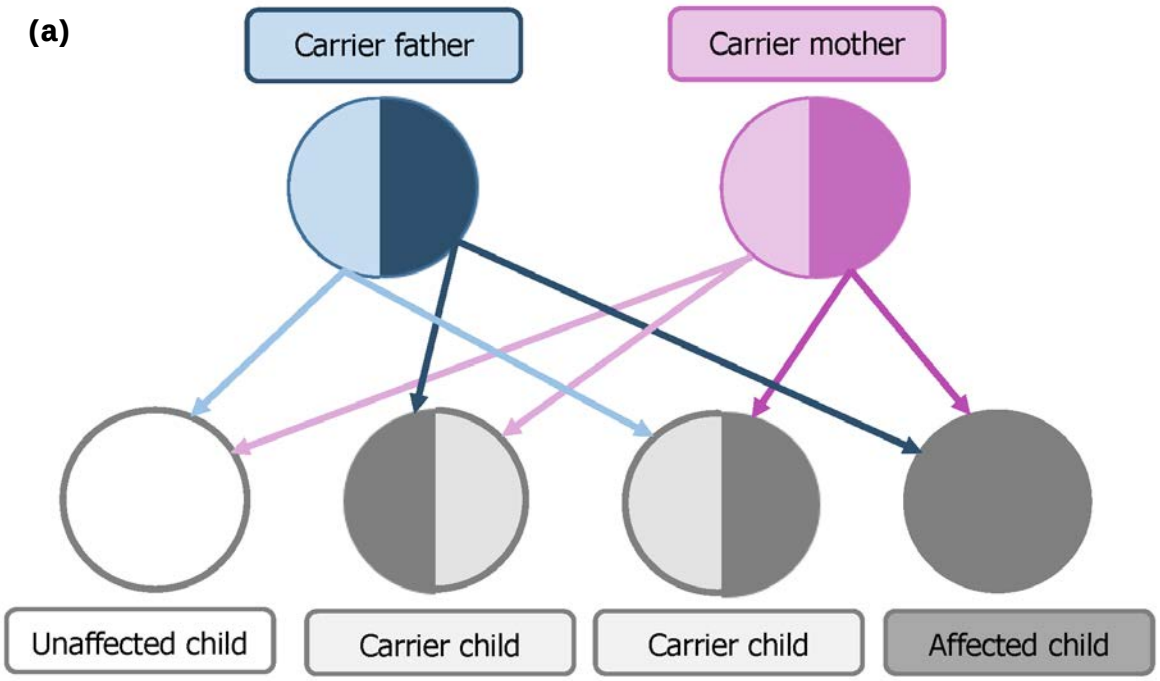
3.1.2 Inheritance pattern

The genetic pattern of inheritance for the majority of the mutations causing SCID is **autosomal recessive**. The typical exceptions are IL2RG mutations, whose inheritance is **X-linked recessive**, and RAC2 mutations, which are **autosomal dominant**.[2] As outlined in Figure 3.3(a), autosomal recessive inheritance means that the mutated gene occurs on one of the 22 non-sex chromosomes contributed by the parent ('autosomal') and occurs when both parents are carriers of the mutated gene ('recessive'). This kind of inheritance equates to a one in four probability that the child will have the condition, a one in two probability that the child will be a carrier and a one in four probability that they will neither have the condition nor be a carrier.[18, 97]

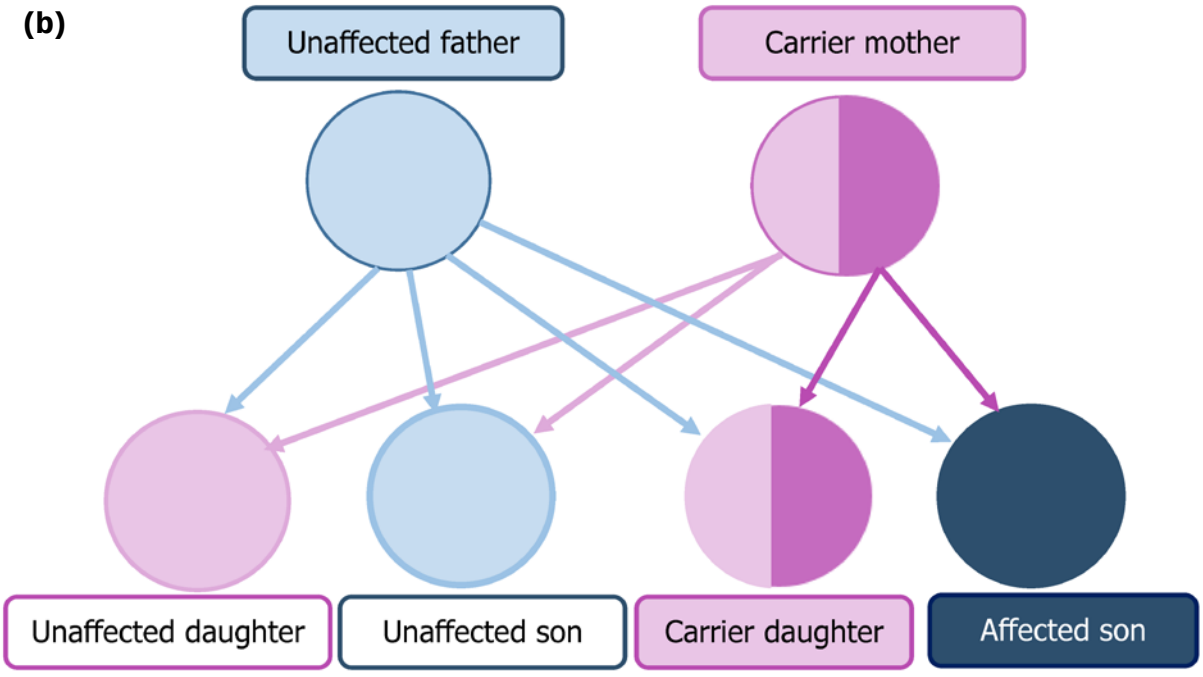
Considering X-linked SCID, as X-linked inheritance means that the mutated gene is located on the X chromosome, and as X-linked SCID is inherited in a recessive manner, this condition occurs almost exclusively in males (as they carry a single copy of the X chromosome). Hence, as shown in Figure 3.3(b), if the father does not have the condition, then the mutation is passed through a carrier mother, resulting in four possibilities: an unaffected son, an unaffected daughter, a carrier daughter, or a son with the condition.[97]

As a result of the genetic patterns of inheritance associated with SCID, overall risk factors include family history and consanguinity.[13] Populations who are geographically isolated or have high rates of consanguineous unions (that is, between individuals who are related) can have a particularly high incidence of autosomal recessive forms of SCID due to founder mutations (that is, a reduced genetic variation that occurs when a new population is established by a subset of individuals from a larger population).[25, 98]

Figure 3.3 (a) Autosomal recessive **(b)** X-linked recessive (unaffected father) inheritance patterns



Note: grey shading indicates a child may be male or female.



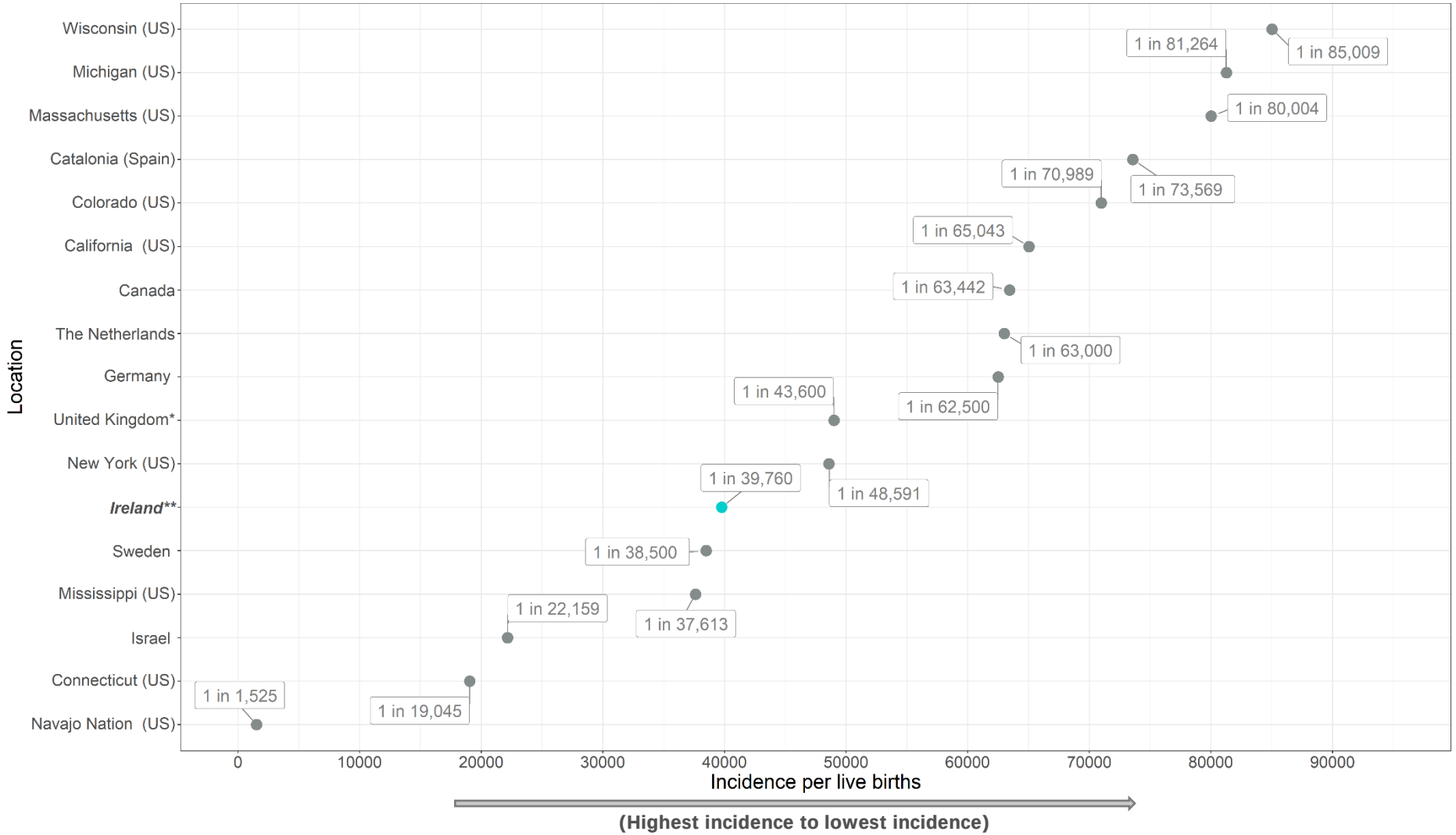
3.2 Incidence of SCID

Given the diversity of genetic mutations associated with SCID, the incidence is noted to vary widely across geographic locations and within certain populations.[25] Estimates of the incidence of SCID have historically been considered to be underestimated. The term birth prevalence is often used in lieu of incidence in the context of congenital disorders; without screening, infant mortality occurring prior to formal diagnosis will not be reflected in the estimates, and as such they likely fail to capture the full extent of rare diseases such as SCID.[6, 99] However, the accuracy of SCID incidence figures is considered to have been positively impacted by the introduction of newborn screening within certain countries; previous underestimates likely resulted from mortality in infants occurring prior to SCID diagnosis.[8, 25] Within Ireland, between 2005 and 2020, there were 27 children diagnosed with SCID.[96] Over this 15-year time period, there were 1,073,519 births registered,[100] reflecting a birth prevalence of **1 in 39,760 births**. Thirteen (48.1%) of the 27 documented cases were of Irish Traveller ethnicity.[96]

Figure 3.4 depicts the population-level incidence of SCID for various countries and regions (including those identified in chapter four), as reported in the academic literature.[91, 101-110] As highlighted, the highest incidence was noted for the Navajo Nation population in the United States, with an incidence of 1 in 1,525 births, based on 6,100 infants screened over a period of 27 months.[107] To note, this population have a notably high incidence of a particular type of SCID (Artemis SCID), owing to a founder mutation in the DCLRE1C gene.[107] The lowest incidence noted by this report was 1 in 85,009 births, as observed from 340,037 infants screened in Wisconsin over a four-year period.[106]

The results of 11 screening programmes in the United States were presented collectively in one study, with the collective incidence estimated to be 1 in 58,000 infants (95% confidence interval (CI): 1 in 46,000 to 1 in 80,000)[106] (results for nine of these programmes are depicted in Figure 3.4; two of the 11 were omitted due to incomplete data). Regarding data from the United Kingdom, it is important to note that the estimate outlined for the UK in Figure 3.4 (1 in 43,600 births) represents unpublished data from 2008 to 2012, which was used to populate an economic model assessing the cost-effectiveness of newborn screening for SCID.[101]

Figure 3.4 Incidence of SCID per live births by location, displayed left to right from highest incidence to lowest incidence



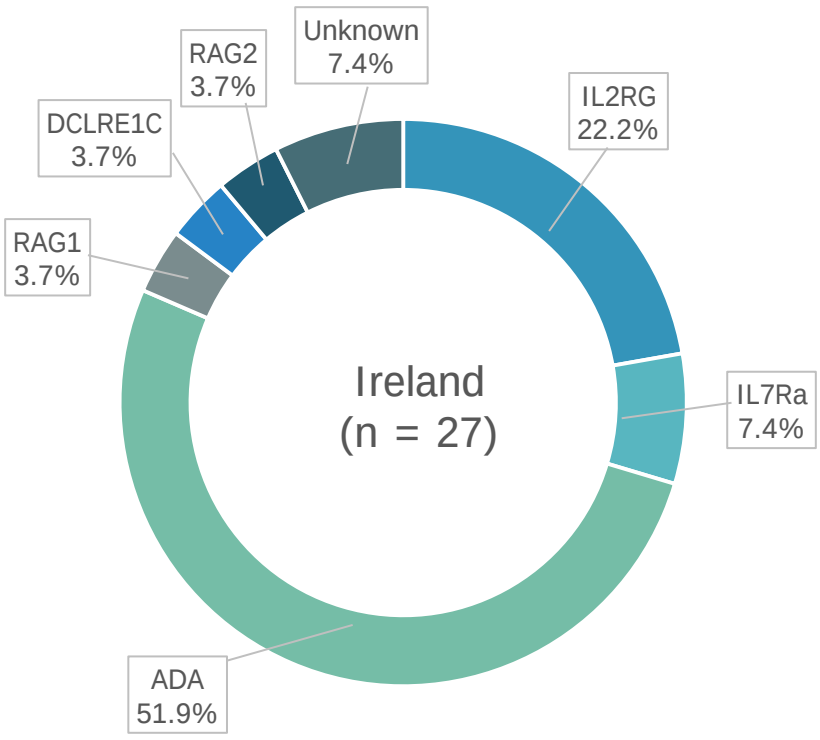
*Estimate provided for economic analysis of screening in United Kingdom, **In the absence of screening in Ireland, the estimate should be considered an underestimate of the true prevalence and should be considered to instead represent birth prevalence. Sources: California (US) - Amatuni 2019[104], Catalonia (Spain) - Argudo-Ramírez 2021[91], Sweden - Göngrich 2021[55], Massachusetts (US) - Hale 2021[105], Navajo Nation (US) - Kwan 2015[107], Israel - Rechavi 2017[108], New York (US) - Vogel 2014[109], Ireland - CHI Crumlin 2021[96], Canada - Rozmus 2013[102], Germany - Shai 2020[103], United Kingdom (estimate) - Bessey 2019[101], The Netherlands - dePagter 2015[110], Colorado (US), Connecticut (US), Michigan (US), Mississippi (US), Wisconsin (US) - Kwan 2014[106].

3.2.1 Molecular basis of SCID

As with the incidence of SCID, the proportional make-up of subtypes, based on genotypes, can vary depending on the population in question.[25] X-linked SCID (IL2RG) is associated with a constant global incidence, accounting for approximately one third of all SCID cases.[25] Differences across locations in the proportions of SCID attributable to different genotypes reflects varying numbers of autosomal recessive subtypes.[25]

Figure 3.5 illustrates the molecular basis of the 27 SCID cases identified in Ireland between 2005 and 2020.[96] Two cases (7.4%) were considered to be atypical SCID, with the remaining 25 (92.6%) being typical SCID presentations. As shown, a considerable proportion were ADA mutations (51.9%, n = 14), followed by IL2RG (22.2%, n = 6), and IL7Rα (7.4%, n = 2). Of the documented ADA mutations, thirteen infants (92.9%) were of Irish Traveller ethnicity.[96] A proportion of cases of ADA-SCID in the Irish Traveller population have previously been attributed to a described founder mutation of the ADA gene (homozygous c.646G > A mutation in exon 7).[6]

Figure 3.5 Molecular basis of SCID cases in Ireland 2005-2020



Source: CHI Crumlin[96]

Figure 3.6(a) illustrates the molecular basis for 52 SCID cases identified across 11 screening programmes in the **United States** as described in a 2014 publication.[106] It should be emphasised that these frequently cited data stem from the 10 states (and the Navajo Nation) in the United States with active screening programmes at the time of the study (as opposed to cases picked up by diagnosis in the absence of screening programmes), with 3,030,083 infants screened within participating programmes from 2008 to 2013. The number of infants screened within individual programmes ranged from 3,498 to 1,384,606, and the duration of reporting ranged from six months to 31 months. The authors highlight that 80.8% (n = 42) of the cases identified met the criteria for typical SCID, while the remaining 19.2% (n = 10) were considered to represent atypical SCID (n = 9) ("leaky"), and Omenn syndrome (n = 1). Of cases with a known molecular basis, the most frequent genotypes noted were IL2RG (19.2%, n = 10), RAG1 (15.4%, n=8), IL-7Rα (11.5%, n = 6) and ADA (9.6%, n = 5). IL2RG mutations further represented the most common cause of typical SCID (17.3%, n = 9) while RAG1 were noted as the most frequent cause of atypical SCID cases presented (40%, n = 4).

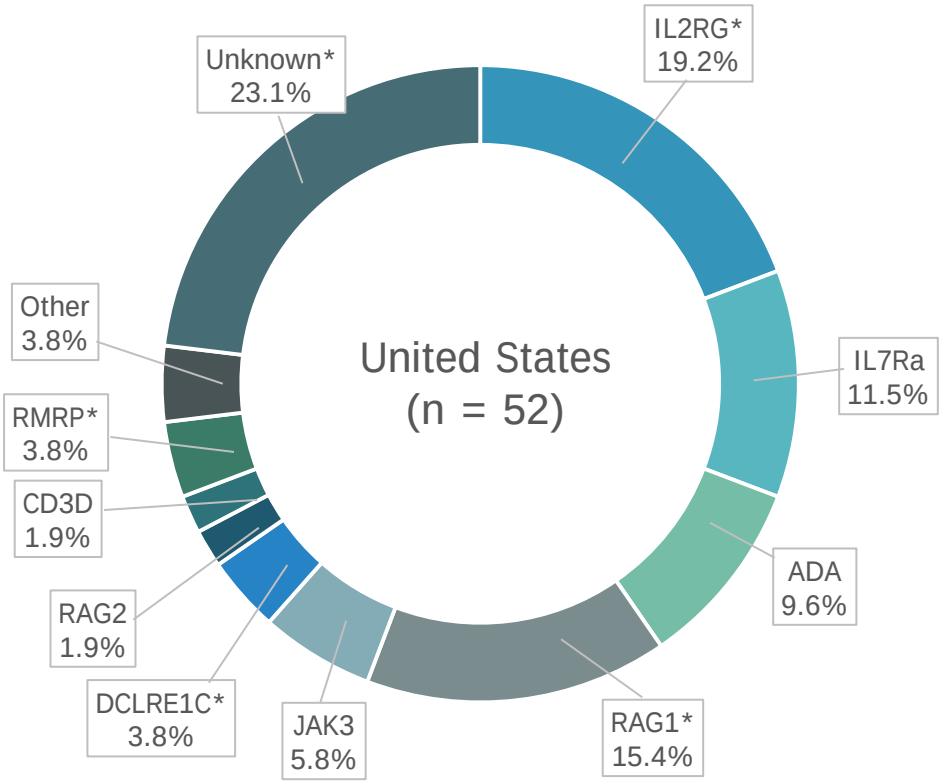
Figure 3.6(b) outlines the molecular basis presented for 142 SCID cases within the **United Kingdom** Primary Immune Deficiency registry from 2012 to 2017.[111] To note, only cases with a defined molecular basis were presented, and the authors did not present a breakdown of typical versus atypical SCID cases. Similar to the United States, IL2RG mutations were noted as the most frequent cause of SCID (32.4%, n = 46), followed by ADA (26.8%, n = 38), RAG1 (10.6%, n = 15) and IL7Rα (9.9%, n = 14).

Figure 3.6(c) illustrates the molecular basis documented for 43 SCID cases in the **Netherlands** over a 15-year period (1998 to 2013).[110] The authors note that 11 (25.6%) cases were considered atypical SCID, but did not provide the associated genotype breakdown. As shown, the most frequent cause of all SCID cases were mutations in the IL2RG (20.9%, n = 9) and RAG 1 (20.9%, n = 9) genes, followed by ADA (11.6%, n = 5).

Collectively, relative to the above locations studied, Ireland presents with a higher proportion of ADA-SCID. Specifically for this subtype, the majority of cases in Ireland are noted to be of Irish Traveller ethnicity.

Figure 3.6 Molecular basis of SCID cases documented in **(a)** United States **(b)** United Kingdom **(c)** The Netherlands

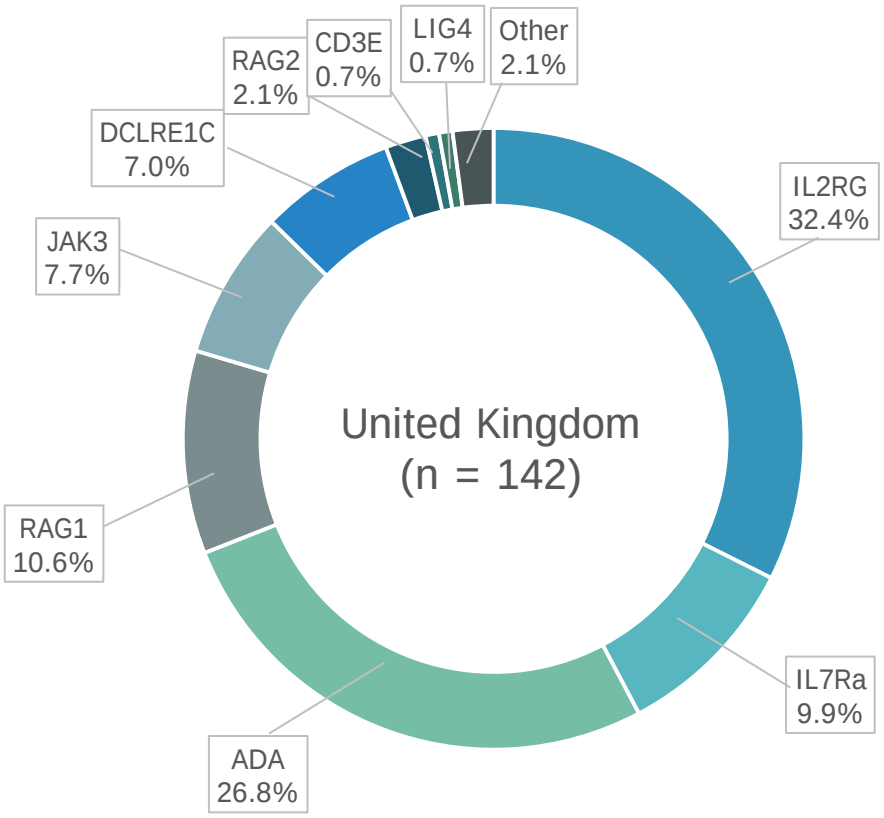
(a)



*Denotes genotype presented for typical and atypical SCID cases. 'Other' includes TC7A and Pallister-Killian syndrome with tetrasomy 12p.

Source: Kwan et al.[106]

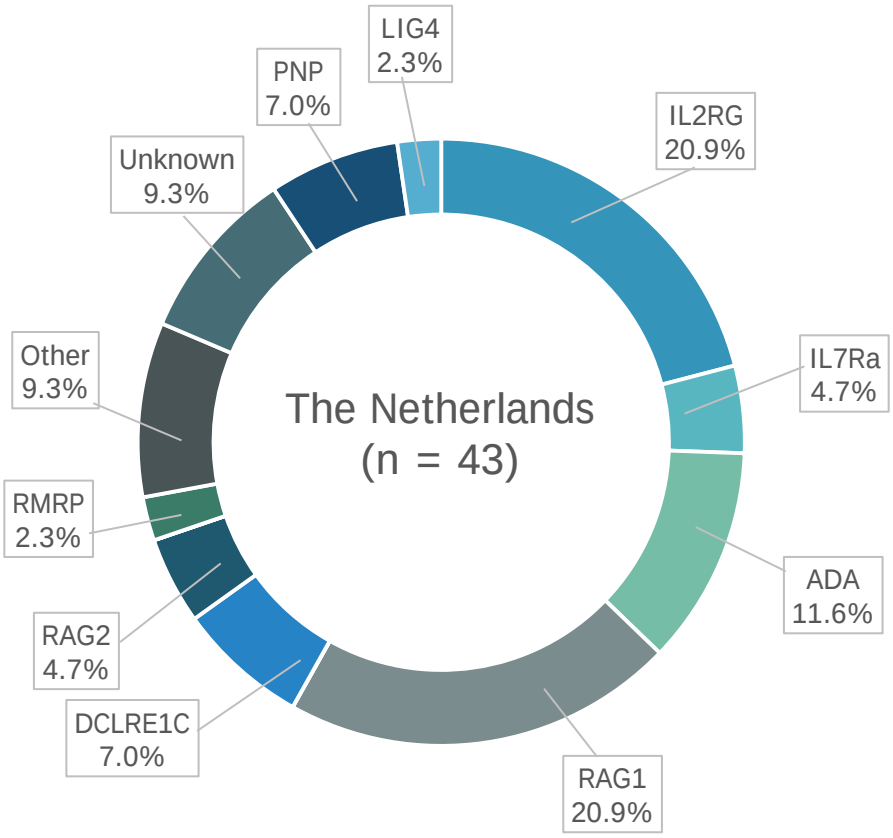
(b)



Note: Only cases with a defined molecular basis presented. 'Other' includes IL-21R.

Source: Shilltoe et al.[111]

(c)



Note: 'Other' includes ZAP70, AK2, CD3E, and T7q-20q.

Source: dePagter et al.[110]

3.3 Clinical presentation and burden of disease

3.3.1 Age at each of symptom onset, clinical presentation, and diagnosis

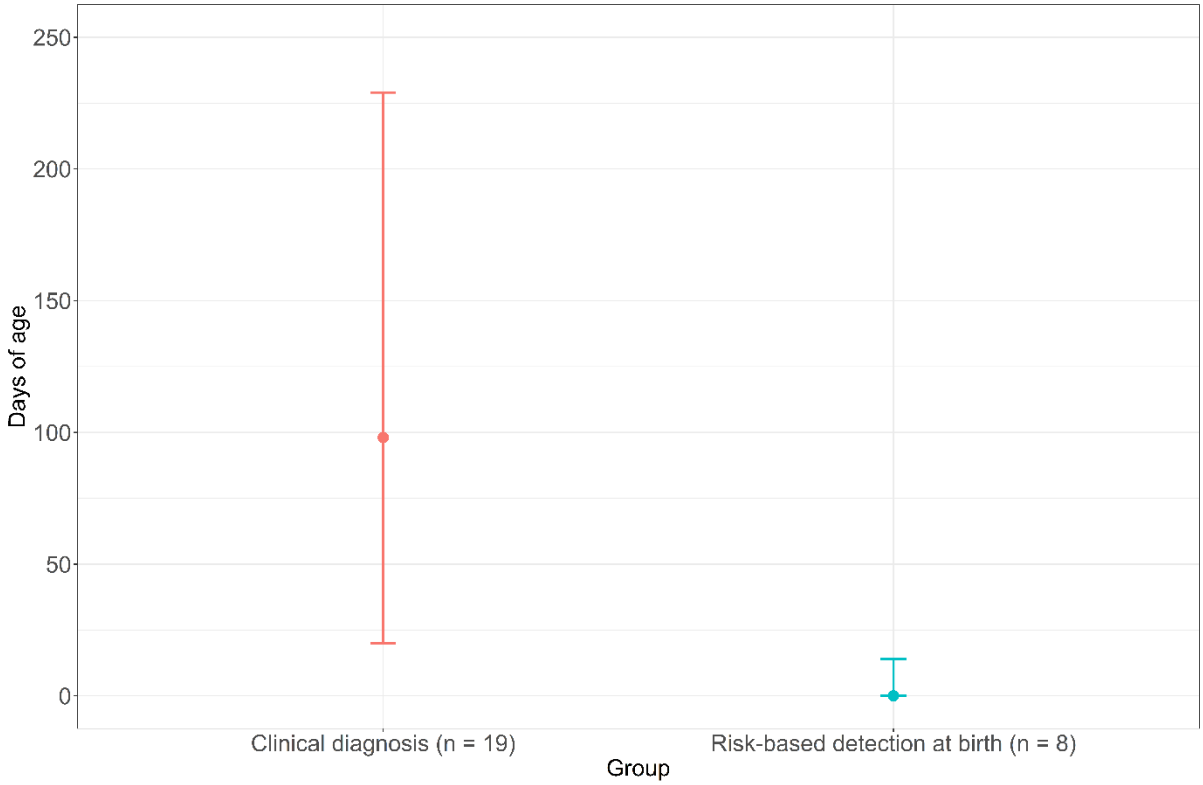
At birth, infants with SCID are typically asymptomatic.[8] SCID may be detected through surveillance based on a known family history, NBS screening, or clinical presentation. From the Irish context, of 27 SCID cases reported between 2005 and 2020, eight infants were diagnosed at birth through risk-based detection (that is, family history or by virtue of Irish Traveller ethnicity) while 19 were diagnosed clinically.[96] Clinical presentation of SCID typically manifests as recurrent and often severe infections, non-infectious health conditions (for example, failure to thrive) and vaccine-derived health problems.[25] In many cases, children will experience multiple infections.[25]

In the absence of a known family history of the condition or an NBS programme for SCID, the time to detection of these cases varies. Of those children diagnosed clinically in Ireland, the median **age at symptom onset** was 33 days and the median age at clinical presentation was 77 days.[96]

According to data from the **German** National Registry of Primary Immunodeficiencies, from 2012 to 2017, clinical onset of symptoms occurred in the first year of life in 86% of SCID cases.[112] Based on German data collected from 2014 to 2015, the median age at diagnosis was 3.5 months (interquartile range (IQR) 1 to 5.5 months).[103] These include a combination of cases detected by family history, symptomatic presentation and, in some cases, screening for SCID. A 2020 report including 20 years of data (1999-2019) from the **Italian** Primary Immunodeficiencies Registry noted the median age of diagnosis of SCID cases to be 0.4 years of age (range 0 to 22 years).[113] Similarly, a **French** primary immune deficiency study group reported a median age of diagnosis of 0.4 years in 2010 based on data collected between November 2005 and April 2009.[114]

There is evidence to suggest that detecting SCID by clinical presentation alone results in a later **age at diagnosis**. In Ireland, the median age for those diagnosed at birth through risk-based detection was 0 days (range 0 to 14) compared with a median of 98 days (range 20 to 229) for those diagnosed clinically (see Figure 3.7).[96] A 2013 study reporting results for 50 patients with SCID from the PIDTC in **North America** found the median age at diagnosis for those with clinical signs of SCID to be 179 days.[115] This compared with a median age of diagnosis of 14 days through NBS screening programmes or those identified for testing based on a positive family history.[115] Furthermore, a 2020 updated publication from the PIDTC reporting on a cohort of 59 patients with SCID noted the median age at diagnosis was 25 days (range 0 to 85 days) for infants diagnosed by NBS screening programmes and 6 days (range 0 to 32 days) for those identified for testing on the basis of a family history of SCID.[116] The wide range associated with age at diagnosis for those diagnosed through NBS screening programmes was attributed to delays in result notification for NBS and confirmatory testing, and some centres not initiating SCID management until additional tests have been completed (such as, T-cell proliferation and maternal engraftment studies).

Figure 3.7 Median and range of age at diagnosis for historical Irish cases (by means of identification)



Note: point represents median, lines represent lower and upper ranges

Variation by subtype

As outlined previously, SCID results from mutations in at least 19 known genes, giving rise to a large number of subtypes. A 2020 publication reporting on data from the **United States** Immunodeficiency Network (USIDNet) concerning **ADA-SCID** patients born between 1981 and 2017 (n = 64) noted a median age of symptom onset of 0.2 years (range 0 to 0.8 years) and median age at diagnosis of 0.3 years (range 0 to 9 years).[117] The same report, however, highlights a reduction in age of diagnosis over time, with patients born after 2010 having a median age of diagnosis of 0.1 years.[117] The report also found that there was no significant difference between mean age at diagnosis for those with or without a known family history when considering ADA-SCID specifically (0.77 ± 1.5 years versus 0.81 ± 1.4 years).[117] From the Irish perspective,[96] excluding those with an ADA-SCID diagnosis specifically (considering that screening for this SCID subtype is, at the time of writing, undergoing implementation), three infants were diagnosed at birth and 10 were diagnosed clinically. For those 10 diagnosed clinically, the associated median ages reported for symptom onset, clinical presentation, and diagnosis were 97 days (range 4 to 171), 145 days (range 4 to 207), and 157 days (range 48 to 229), respectively.

Cases of **leaky SCID** are typically associated with a later onset of symptoms and greater delay in diagnosis. A 2015 Dutch study reported on a cohort of 43 SCID cases in the Netherlands over a 15-year period.[110] The authors note a median time of two months after onset of symptoms for diagnosis of typical cases of SCID compared with a median of 27 months for leaky SCID.[110] Likewise, a recent updated publication by the US PIDTC, on a cohort of 662 SCID patients diagnosed between 1982 and 2012, reported that typical SCID cases had a median age at diagnosis of 140 days (range 30 to 209 days), whereas for cases of leaky SCID the median age at diagnosis was 161 days (range 67 to 256 days).[118] In a 2013 publication considering the same cohort, these leaky SCID cases were more likely to be diagnosed by clinical presentation.[115]

3.3.2 Infectious presentations

Infections in children with SCID can include common **bacterial and viral infections** as well as **opportunistic fungal infections**. Typically, these infections result in lower respiratory tract infections (LRTI), upper respiratory tract infections (URTI) or gastrointestinal infections.[119] A Canadian national surveillance study published in 2013 noted 90% of SCID cases as having one or more infections prior to treatment.[102] A 2020 report by the USIDNet Registry observed 187 infections in 50 patients with ADA SCID,[117] with LRTIs the most common, including 44 episodes of pneumonia recorded in 32 patients and three episodes of bronchiolitis in three patients.[117] In addition, 60% of reported LRTIs occurred before a diagnosis of SCID was made. URTIs and infectious diarrhoea were the next most common types of infection, with 21 episodes in 20 patients and 19 episodes in 15 patients, respectively.[117] Similar patterns of infections were noted in a 2019 report of findings from 57 patients with SCID in India. The authors reported the most common infections to be pneumonia (66%), chronic diarrhoea or gastrointestinal infection (35% and 21%), and oral fungal infections (oral candidiasis, 21%).[120] Moreover, three additional publications noted fungal infections as the most frequent opportunistic infection in their respective cohorts of SCID patients. A 2013 publication from the United States including 50 children with SCID reported 31% of infections to be fungal, caused by *Candida* species and *Pneumocystis jirovecii*.[115] *Pneumocystis jirovecii,* the cause of *Pneumocystis* pneumonia (PCP), was also reported as the most frequent cause of infection in a German cohort of 22 SCID cases, accounting for the seven of 12 cases of infections and in a US cohort of 240 SCID cases, causing 61 cases of PCP.[103, 121] In a 2013 publication reporting on cases of SCID identified by the Canadian Paediatric Surveillance Program (CPSP) between 2004 and 2010, detailed documentation of infections was available for the full cohort of 40 SCID patients, with one or more infections recorded in 36 patients.[102] There were 13 cases of viral infections, most frequently caused by

cytomegalovirus (CMV) (n = 6), respiratory syncytial virus (n = 2) and adenovirus (n = 2). There were eight cases of bacterial infections, six of which resulted in bacteraemia and two resulting in pneumonia. Fungal infections were the most common type of infection, with eight cases of superficial candidiasis, six instances of PCP and one case of *Rhodotorula mucilaginosa* osteomyelitis.[102]

A 2017 US PIDTC publication found that 92% of patients diagnosed clinically had an infection prior to HSCT, compared with 42% of patients identified on the basis of NBS or family history.[122] In a cohort of 43 patients with SCID in the Netherlands diagnosed between 1998 and 2013, there were 71 documented infections prior to treatment. Forty-seven of these infections occurred in 34 children who survived to HSCT or gene therapy.[110] The most common infections in this cohort were bacterial sepsis (n = 11), PCP (n = 11), other causes of pneumonia (n = 19), and systemic CMV infection (n = 8). There were 24 documented infections in nine children who did not receive treatment, with the most common being bacterial sepsis (n = 8).

Across the 27 SCID cases in Ireland, 47 documented infections were noted prior to treatment (with HSCT or gene therapy), with three occurring in the group of eight diagnosed at birth and 44 in the group of 19 diagnosed clinically, illustrating clear instances of multiple infections for a number of infants.[96] Excluding those with a diagnosis of ADA-SCID, all remaining 32 documented infections prior to treatment were in those who were diagnosed clinically.

3.3.3 Non-infectious presentations

In addition to severe infections, individuals with SCID may also experience non-infectious complications due to the absence, depletion, or dysfunction of T-cells and or secondary to their specific SCID-subtype. These complications include growth delays or insufficient weight gain, termed failure to thrive.[117, 119] Failure to thrive is consistently reported as one of the most frequent non-infectious health complications experienced by infants with SCID, reported to affect between 21% and 60% of SCID cases in several publications.[102, 103, 118, 120, 123, 124]

ADA-SCID can be associated with marked neurological and physiological abnormalities, due to organ dysfunction and damage associated with metabolite accumulation, separate to infection.[117] The USIDNet report found that 49% of patients with ADA-SCID experienced neurologic conditions, including hearing loss and coordination disability; 67% presented with gastrointestinal conditions such as diarrhoea and gastroesophageal reflux; and 30% had one or more pulmonary condition such as asthma, bronchiolitis or interstitial lung disease.[117]

Unlike typical SCID where T-cells are absent or severely reduced in number, **Omenn syndrome,** which results from hypomorphic genetic mutations, involves normal or

increased numbers of T-cells. However, the T-cells observed in Omenn syndrome represent an oligoclonal population (that is, the cells are direct clones and are therefore highly restricted in repertoire) and are self-reactive; these T-cells infiltrate the skin, liver, gut and other organs, causing serious damage to these organs.[125] Patients with this condition can present in the first weeks of life with erythroderma (severe rash or dermatitis), enlarged lymph nodes, hepatosplenomegaly (swollen liver and spleen), eosinophilia (abnormally high number of eosinophil immune cells) and severe hypogammaglobulinaemia (severely low immunoglobulin G).[125] In a cohort of 90 patients with SCID in France treated with HSCT between 1972 and 2004, there were eight cases of Omenn syndrome and 12 cases of maternofoetal engraftment, also referred to as Omenn-like syndrome.[123] In addition, from the period 2009 to 2018, there were an additional 15 cases of Omenn syndrome recorded by the French national reference center for primary immunodeficiencies (CEREDIH) .[82] Between 2014 and 2018, the average age at diagnosis for these cases of Omenn syndrome was 1.3 months, compared to 3.6 months for typical SCID cases.[82]

Non-infectious complications documented for the Irish cohort of SCID patients included failure to thrive (n = 14), Omenn syndrome (n = 1), encephalopathy (n = 1), malignancy (n = 1), and retinopathy (n = 1), with ADA-SCID specific complications including nine instances of pneumonitis and five of cardiomyopathy.[96] Of note, all 14 instances of failure to thrive were infants who were diagnosed clinically as opposed to at birth, with eight of these being SCID diagnoses for subtypes other than ADA-SCID.

3.3.4 Vaccine-specific complications

There are important interactions with childhood vaccination programmes whereby children with SCID should not receive **live viral or bacterial vaccines** (for example, BCG and rotavirus).[9, 39] A 2014 publication reported on outcomes associated with BCG vaccination in a cohort of 349 SCID patients from 17 countries who received the vaccine.[9] The majority of patients were vaccinated within one month of birth (75%). Complications were experienced by 177 patients; of these, 59 patients experienced localised complications while 118 experienced disseminated BCG infection (BCGosis). This represents a considerable increase in vaccine-associated complications compared with the general population.[9] Additionally, several case reports of patients with SCID who received a vaccine for rotavirus outline complications such as diarrhoea, vomiting, and failure to thrive, often leading to hospitalisation.[126-129]

From the Irish context, nine infections secondary to live vaccination were documented across the 27 SCID cases from 2005 to 2020. All of these occurred in

those who were diagnosed clinically, with three infections occurring among those with ADA-SCID.[96]

3.3.5 Survival to definitive treatment

Data on survival to definitive treatment were identified from a number of countries internationally. Heterogeneity was noted in terms of years of data collection, health systems, and patient demographics:

- Of the documented Irish cohort from 2005 to 2020 (n = 27), a total of 25 (92.3%) children survived to definitive treatment, with both cases of mortality being in the group diagnosed clinically and neither occurring in those with ADA-SCID.[96]
- A 2015 publication from the Netherlands reported on a cohort of 43 SCID patients between 1998 and 2013, in which 34 (79.1%) children survived to definitive treatment. Of nine patients who did not survive, eight died at a median of 12 days (range 0 to 88 days) after initial infectious presentation and despite antimicrobial treatment.[110]
- A 2019 report from India noted that from a total of 57 infants with SCID, 43 did not receive HSCT treatment and did not survive. The median age of death for these infants was six months (range 1.5 to 36 months) with the majority of mortality occurring before 12 months of age (n = 38).[120] Sepsis, respiratory failure and chronic diarrhoea were reported as the most common cause of deaths in this cohort.
- A Canadian national surveillance study published in 2013 reported seven deaths prior to treatment from a cohort of 40 SCID cases; the listed causes of death were as follows: encephalitis, lymphoma, influenza, disseminated cytomegalovirus and acute neurological event, myeloproliferative syndrome, cytomegalovirus pneumonitis and multi-organ failure, and disseminated cytomegalovirus and respiratory failure.[102]
- Of the 64 patients with ADA-SCID reported from USIDNet data in 2020, four died prior to the receipt of HSCT. The causes of deaths were pneumonia (n = 1), septic shock and respiratory/cardiorespiratory failure (n = 1), uncontrolled haemolytic anaemia (n = 1), and, in one patient's case, unknown.[117]
- In addition, according to the CEREDIH registry in France, between 2014 and 2018, mortality for SCID in the absence of treatment was 100%; of 42 SCID cases, seven cases died having not received a transplant while 34 survived to transplant, with an additional seven cases of Omenn syndrome (categorised

separately to SCID within the report) also surviving to transplant.[82] An additional patient with SCID was an ADA-SCID case and was in receipt of enzyme replacement therapy, but had not undergone a transplant.

Survival outcomes following treatment are described separately in section 3.3.12, below.

3.3.6 Age at definitive treatment

Given the heterogeneous nature of the condition and the various methods of identification, the age at treatment for children with SCID varies; however, it is often linked with age at diagnosis (that is, earlier diagnosis results in earlier treatment). By necessity, given the emergency nature of the condition, treatment for SCID is carried out as early as possible. Data relating to age at definitive treatment were noted from a number of sources internationally:

- Collectively, across the 27 SCID cases documented in Ireland from 2005 to 2020, the median age at definitive treatment was 119 days (range 24 to 354).[96] For those diagnosed through risk-based detection at birth, the median age was 54 days (range 24 to 258) compared to 184 days (range 67 to 354) for those diagnosed clinically (see Figure 3.8). Of note, these differences remain similar when considering only those without an ADA-SCID diagnosis (at birth: 50 days, clinically: 204 days).

- A 2012 publication by the Center for International Blood and Marrow Transplant Research (CIBMTR), examining 450 transplant centres internationally, reported that 97% of patients with SCID received HSCT before two years of age.[130]

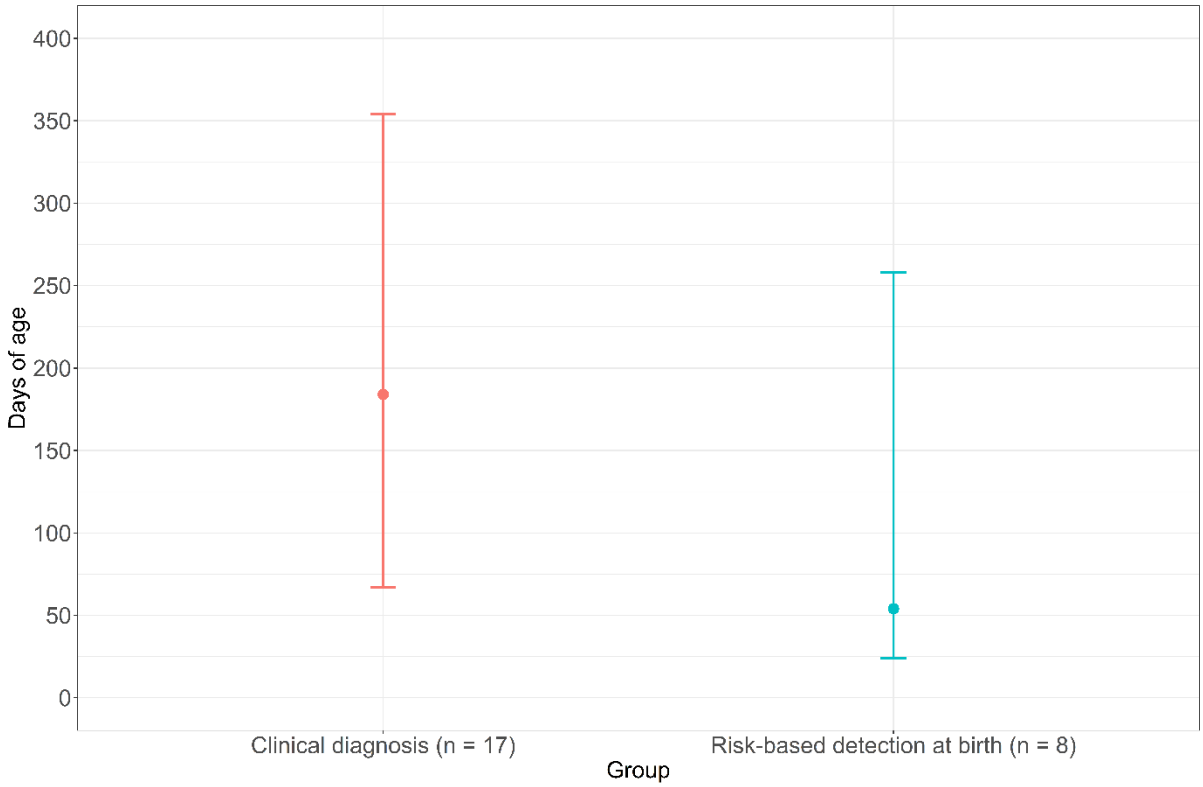
- A 2013 publication by the US PIDTC reports a younger median age at time of treatment for those diagnosed through NBS or family history compared to those diagnosed by clinical symptoms (median age at time of treatment 67 days and 214 days, respectively).[115]

- Similarly, a 2014 publication, reporting on a cohort of 240 infants with SCID in the US, notes that those with a family history of SCID were more likely to have received treatment by 3.5 months of age compared to those without a family history of the condition (85% vs 13%).[121]

  In terms of variation by subtype, a 2018 report from the US PIDTC presented an analysis of SCID patients between 1982 and 2012 and found a significant difference in the age at treatment for those with typical SCID compared with leaky SCID. The median age at time of HSCT for those with typical SCID was

187 days (IQR, 101 to 264 days) versus 222 days (IQR, 112 to 381 days) for patients with leaky SCID.[118]

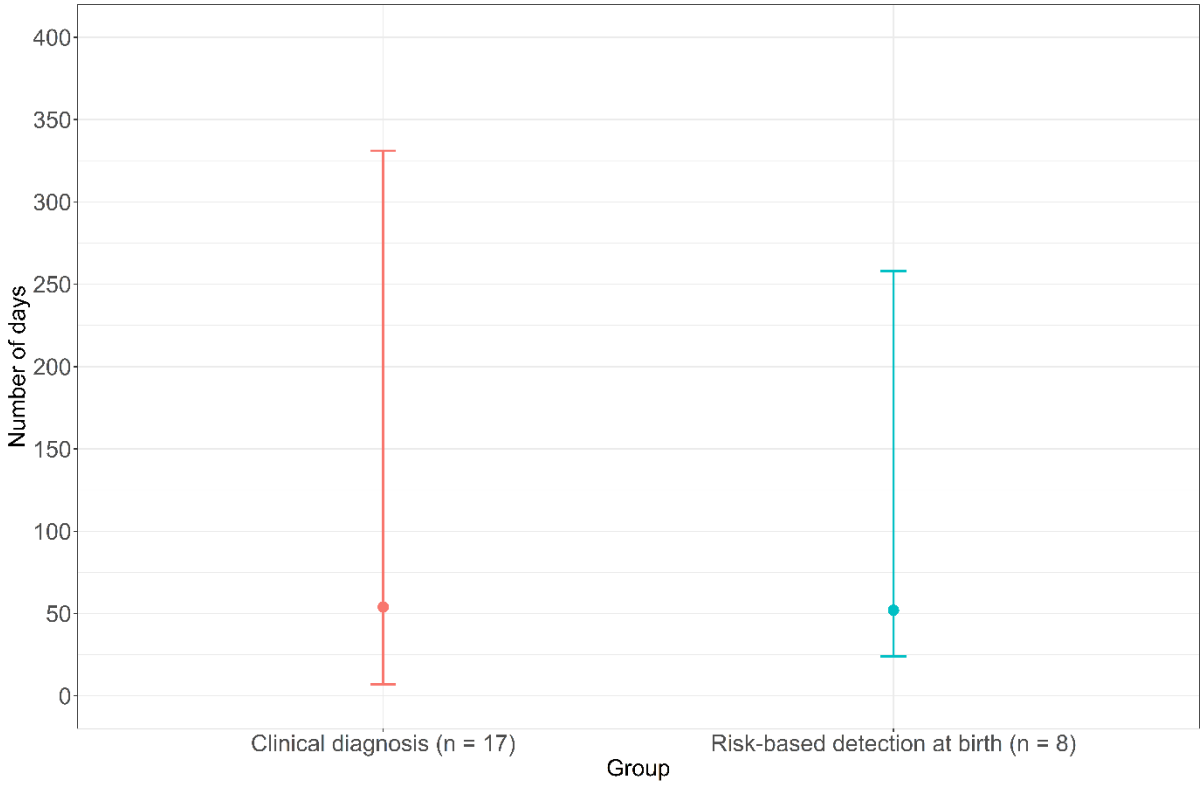
Figure 3.8 Median and range of age at definitive treatment for historical Irish cases (by means of identification)



Note: point represents median, lines represent lower and upper ranges

As shown in Figure 3.9, within the Irish cohort, the time from diagnosis to definitive treatment was similar for those identified through risk-based detection at birth (median 52 days, range 24 to 258) compared to those diagnosed clinically (median 54 days, range 7 to 331).[96] Considering the sub-group of non ADA-SCID diagnoses, the time from diagnosis to definitive treatment was similar, with a median of 50 days (range 50 to 53 days) for those diagnosed at birth and of 49 days (range 32 to 86) for those diagnosed clinically. According to the CEREDIH registry for primary immunodeficiencies in France, the median time from diagnosis to treatment was 0.2 years (IQR, 0.1 to 0.3 years) in a cohort of 201 patients with SCID.[114] Similar findings were reported in a 2013 publication by the US PIDTC, in which the authors noted that the median time from diagnosis to treatment was two months,[115] with no significant differences between those diagnosed by NBS or family history compared with clinical presentation alone (median time from diagnosis to treatment of 56 days and 43 days, respectively).

Figure 3.9 Median and range of time from diagnosis to definitive treatment for historical Irish cases (by means of identification)



Note: point represents median, lines represent lower and upper ranges

3.3.7 Infection status at time of treatment

As previously discussed, the immunodeficiency associated with SCID leaves the patient susceptible to infection. As a result, many infants with the condition may have acquired one or more infections prior to treatment and furthermore may have an active infection at the time of treatment which may further impact on overall treatment outcomes.[121] A 2018 US PIDTC publication reported 77.3% (n = 512) of the cohort they reviewed (SCID patients receiving treatment between 1982 and 2012) had experienced infection at or before transplant, with 47.1% (n = 312) experiencing an active infection at the time of transplant.[118] A 2017 PIDTC publication found that 54% of patients diagnosed clinically had an infection at the time of HSCT compared to 27% of patients identified on the basis of NBS screening or family history.[122] From the Irish cohort, 15 (55.6%) patients had an active infection at the time of definitive treatment (HSCT or gene therapy), all of whom were infants who were diagnosed clinically.[96]

3.3.8 Hospital admission prior to treatment

A 2020 retrospective analysis of data from the US PIDTC collected between 2010 and 2014 reported on the management of 59 patients with SCID at PIDTC-reporting centres.[116] The authors found that 36 infants were hospitalised continuously following their SCID diagnosis, while 23 infants were managed as outpatients. Incidence of infection was not found to differ between these two groups (47% and 35%, respectively; p=0.423).[116] A 2019 publication on NBS screening for SCID in California reported data on neonatal intensive care unit (NICU) admissions for patients with SCID between August 2016 and March 2017. The authors noted that five patients required NICU admission out of a total of 49 patients with SCID; all five patients in NICU were classified as typical SCID cases.[104] From the Irish context, of the 27 children diagnosed with SCID between 2005 and 2020, 11 required admission to a paediatric intensive care unit (PICU) prior to definitive treatment (with a typical length of stay of approximately 16 days), with all being from the group of children diagnosed clinically.[96]

3.3.9 Treatment type

As noted previously in section 2.3.4, HSCT remains the gold standard for the treatment of SCID overall, while additional treatment options are available when considering ADA-SCID specifically (that is, enzyme replacement therapy and gene therapy) in the absence of matched family donors. Given this hierarchy, HSCT remains the most common treatment type; a 2018 US PIDTC publication reported that 93% of 662 patients included in their analysis had received HSCT as their initial treatment for SCID.[118] In terms of donor origin, mismatched family donor (MMFD) was recorded as the most common donor origin (n = 413, 62%) followed by mismatched unrelated donor (MMUD) (n = 130, 20%), matched sibling donor (MSD) (n = 91, 14%) and matched family donor (MFD) (n = 28, 4%).[118] Similarly, of 90 SCID patients treated with HSCT in France, the majority of donors were noted to be of MMFD origin (57%).[123] As highlighted, enzyme replacement therapy is a treatment option for ADA-SCID specifically and is most commonly used as a bridging therapy prior to HSCT or gene therapy. Data from the USIDNet registry indicate that 70% of ADA-SCID patients born between 1981 and 2017 received enzyme replacement therapy; where data were limited to patients born between 2010 and 2017, this figure increased to 88%.[117]

Of the 25 documented SCID cases in Ireland from 2005 to 2020 who survived to treatment, 21 were treated with HSCT (with one receiving a second transplant, see below) and four cases of ADA-SCID were treated with gene therapy (under clinical trials at Great Ormond Street Hospital, London).[96] Of the 14 documented cases of ADA-SCID, nine (64.3%) received enzyme replacement therapy (ERT) as bridging

therapy. Of the 22 instances of HSCT, the donor types were MFD (n =7), MSD (n = 5), umbilical cord blood (n = 4), MUD (n = 3), and haploidentical (n = 3). Considering conditioning, 10 transplants were not associated with a conditioning regimen prior to HSCT.

3.3.10 Requirement for stem cell boosts or additional transplants

In some cases, treatment with HSCT may not achieve the desired outcomes; there may be ineffective recovery of haematopoiesis (resumption of the formation of blood cells) or ineffective immune reconstitution (the rebuilding of the immune system post transplant), both of which represent 'graft failure'. In such cases, patients may be treated with an additional dose of donor cells (stem cell boost) or undergo a full additional transplant. Here, stem cell boosts typically refer to an additional infusion of stem cells from the same donor without conditioning, whereas an additional transplant involves HSCT from a different donor with or without conditioning, or from the same donor with conditioning.[121, 131] In Ireland, of the 21 children with SCID who have received HSCT up to 2020, one received a second HSCT.[96]

A 2013 US retrospective study reporting outcomes for SCID patients reported that 28.7% (n = 49) of 171 patients received one to three subsequent transplants, with 29 receiving stem cells from the same donor source and 20 from a different donor source.[132] A 2009 study, also based in the US, focusing on long term outcomes following HSCT reported similar findings, with 25% (n = 28) of 161 included patients requiring what was referred to as a booster transplant.[133] A 2009 study based on patients (n = 90) treated in a French hospital between 1972 and 2004, reported that 12% (n = 12) of patients required a 'booster'; while described as 'booster transplants' within the study, a number of these subsequent transplants were noted to involve conditioning.[123] A retrospective analysis of 181 Japanese children who received HSCT for SCID between 2006 and 2016 noted that 16 cases (9%) required a subsequent transplant (including both booster and second HSCT) with a median interval between initial and subsequent transplant of 127 days (range 31 days to 6.1 years).[131]

The aforementioned 2013 US study also notes that the survival rate in patients who required a subsequent transplant was 63% (n = 31) compared with 80% (n = 98) in those who did not .[132] A 2009 study focusing on long term outcomes of SCID patients highlighted that transplantation within the first 3.5 months of life led to higher long-term survival, better nutritional status and fewer subsequent booster transplants.[133] This finding is supported by a 2013 US study reporting that among patients who required a subsequent transplant, the average age at initial transplantation was 223 days versus 165 days for those not requiring a subsequent

transplant.[132] These issues will be further explored in chapter five of this report, which specifically reviews outcomes associated with early versus later HSCT.

3.3.11 Post treatment complications

Some patients may experience complications post HSCT. A commonly reported complication experienced by patients following HSCT is acute or chronic graft-versus-host disease (GvHD). This is where donor T-cells cause pro-inflammatory responses in the host upon encountering host cells that these donor T-cells regard as hostile.[134] Common symptoms of acute GvHD include a rash, usually initiating at the extremities such as the palms of the hands or the soles of the feet (also commonly manifests on the shoulders or the ears), jaundice, swelling of the liver, and diarrhoea.[135] Other symptoms include anaemia, thrombocytopenia, and fever.[135] Symptoms of chronic GvHD can be similar to acute GvHD but may also include: hair loss, dysphagia, cirrhosis, dry eyes, wheezing and persistent cough, and muscle inflammation.[134] GvHD complications are a significant cause of transplant-related morbidity and mortality in these patients. GvHD complications within the first 100 days following HSCT are classified as acute, while those that arise after this time period are considered chronic.[135]

Reporting on data collected between 1982 and 2012, the PIDTC found that the cumulative incidence of moderate or severe (Grade 2+) acute GvHD was 23% (95% CI, 20 to 27%), while chronic GvHD at five years after transplant was 16% (95% CI, 13 to 19%).[118] Acute GvHD was found to be more common than chronic GvHD in a 2012 publication by the Center for International Blood and Marrow Transplant Research, which reported on 23 years of data for 201 patients with SCID across a range of international treatment facilities.[130] The report found that 37% of SCID patients experienced moderate or severe (Grade 2+) acute GvHD after treatment, compared with 16% who experienced chronic GvHD, although GvHD resolved for one third of this group by two years post-transplant.[130] Likewise, a French study reporting transplant outcomes for 90 patients with SCID from 1971 to 2004 found that 31% of those who underwent transplant experienced moderate or severe (Grade 2+) while 27% of patients experienced chronic GvHD by two years after treatment.[123] Moreover, according to a report of data from the Stem Cell Transplantation for Immunodeficiencies in Europe (SCETIDE) registry in 2021, approximately 39% (n = 126) of patients with SCID experienced acute GvHD following HSCT.[136] Of these, 69% (n = 87) experienced moderate or severe (Grade 2+) acute GvHD, though life-threatening (Grade 4) GvHD was infrequent (5.6%). Within the Irish cohort, following HSCT, seven patients were diagnosed with acute GvHD with all but one case experienced in children diagnosed clinically as opposed to at birth.[96] Additional complications noted within the Irish cohort included cases of pulmonary haemorrhage, cerebral palsy, and the need for liver transplant.

Some patients may experience long term or persistent complications post HSCT. Persistent diarrhoea (lasting longer than one year) as well as autoimmunity were recorded by a 2009 study as severe events occurring after HSCT.[123] Persistent diarrhoea was identified in 32% of patients (n = 29), which was further separated into those with GvHD (22%, n = 20) and those without GvHD (10%, n = 9), while autoimmunity was reported in 7% of patients (n = 6).[123] According to a 2014 report from the Netherlands, 24 out of 32 patients underwent successful HSCT. Of these patients, 11 experienced infectious complications after transplant and two patients had allo-reactive complications.[110]

3.3.12 Survival post-treatment

A detailed systematic review assessing the outcomes of early versus late HSCT for SCID will be presented in section 5 of this report.

Of the documented Irish cohort, 24 (96%) of the 25 children who underwent treatment (21 undergoing HSCT and four gene therapy) were alive at 24 months follow-up, with one death prior to six months follow-up, which occurred in an infant diagnosed clinically. All surviving 24 cases were considered to have achieved T-cell reconstitution, with 17 infants having B-cell reconstitution.[96]

A 2012 CIBMTR publication reported the probability of overall survival for SCID at seven years post treatment as 93% (95% CI 89 to 97). However, it is important to note that this study focused exclusively on patients who had survived at least two years post transplantation, which, as a result, excludes the period of time in which patients are at most risk of post-transplant complications.[130] A 2014 US study reported an overall survival of 87% (n = 45) for patients who received transplant, gene therapy and or enzyme replacement therapy (the latter specifically in the case of ADA-SCID); however, the time point to this outcome was not reported.[106] A study of SCID patients treated in a US medical centre between 1982 and 2008 (n = 161), reported lower overall survival of 77% (n = 124) at a median follow-up of 8.7 years post transplant (range six months to 26 years); however, it did find a significant difference in survival outcomes depending on age at transplant, with 96% (n = 45) of patients transplanted at or before 3.5 months surviving (median follow up 9.2 years) compared to 70% (n = 79) of patients transplanted after this age (median follow-up 8.5 years).[133]

The PIDTC in the US noted in a 2018 publication that the ten year overall survival for SCID patients following treatment with HSCT was 71% (95% CI 67 to 74).[118] The authors reported that donor type impacted survival, with patients receiving a transplant from a MSD experiencing survival rates of 94% at 10 years (95% CI 87 to 98 at 10 years), which was statistically higher when compared to other donor

types.[118] In addition, infection status at time of transplant was found to significantly affect survival of patients aged greater than 3.5 months of age at time of transplant, but not those younger than 3.5 months at time of HSCT. Of note, among patients with active infection at time of transplant, survival was better in those aged younger than 3.5 months at time of HSCT compared to those who were older (hazard ratio HR 0.29; 95% CI 0.11 to 0.74). These results are in agreement with a 2014 publication reporting on the same cohort between 2000 and 2009. This earlier report found that age and active infection at time of transplant were strongly associated with a lower survival rate. The highest survival outcomes were among patients without previous infection history and aged less than 3.5 months at time of transplant (94% survival based on 64 patients surviving to ten years post-transplant from 68 treated). In contrast, the poorest survival outcomes were among patients with active infection at time of treatment and aged greater than 3.5 months at transplant (50% survival based on 45 patients surviving from 91 treated). It should be noted that infants aged greater than 3.5 months at time of transplant who had no history of infection prior to treatment had good survival outcomes following HSCT (90% survival based on 21 patients surviving from 23 treated).[121]

Furthermore, a 2021 publication from the SCETIDE registry noted that pre-transplant infections had a strong negative impact on survival outcomes.[136] The two-year overall survival was lower in infected (73%; 95% CI 66 to 80) compared with uninfected individuals (86.6%; 95% CI 82 to 92). A similar relationship was seen for two-year event free survival, with this metric lower in patients with infections (65.5%; 95% CI 58 to 74) compared with patients without pre-transplant infections (79.9%; 95% CI 75 to 86). Similar associations were reported by the CEREDIH registry in France for patients treated between 2010 and 2018, with increased mortality among SCID cases with infections prior to transplant (29%) compared with those without pre-transplant infections (13%).[82] The authors noted the difference not to be statistically significant, likely due to small sample size, and the follow-up time was unclear.

3.3.13 Causes of mortality post-treatment

In terms of the causes of mortality following treatment for SCID, a 2018 PIDTC publication reported that of 194 deaths which occurred after HSCT, 55% (n = 107) were caused by infection; 11.8% (n = 23) were due to pulmonary or acute respiratory distress syndrome; 7.7% (n = 15) were due to GvHD; 4.1% (n = 8) were linked to central nervous system; 3% (n = 6) were caused by multiple organ failure, and the remainder of deaths were attributed to a range of other complications, including one cause of death noted to be related to the procedure.[118] This study also outlined causes of death in relation to ADA-SCID specifically (n = 12), with 53% (n = 8) attributed to infection, 13% (n = 2) caused by

pulmonary/acute respiratory distress syndrome, 6.6% (n = 1) relating to central nervous syndrome, and 6.6% (n = 1) as a result of multiple organ failure).[118]

A study reporting on data collected on 161 SCID patients who received HSCT between 1982 and 2008 recorded 37 deaths, with causes including viral infections (75.6%, n = 28), pulmonary disease (10.8%, n = 4), and *Candida* bloodstream infection (5.4%, n = 2). Single instances of an unrelated mitochondrial defect, nephrotic syndrome, and veno-occlusive disease were further reported.[133]

The primary causes of death between two and six years post-transplant, as reported by the CIBMTR in 2012, were chronic GvHD (n = 2), infection without GvHD (n = 3), organ failure (n = 3), and post-transplant lymphoproliferative disease (n = 1).[130] A 2009 publication reporting on long term outcomes of HSCT in France found that eight patients suffered late mortality between 2.5 and 11 years post transplantation; cited causes were poor immune reconstitution, chronic GvHD and related complications, viral meningoencephalitis, and myelodysplasia complicated by acute myeloid leukaemia.[123]

3.4 Discussion

The purpose of this chapter was to outline the epidemiology associated with SCID, including the aetiology, incidence, and clinical presentation of the disease, and burden of disease, drawing on international and national data. To note, while the focus of the chapter was SCID in its entirety, an effort was made to distinguish cases of ADA-SCID where possible, particularly when considering the available Irish data. This reflects the change to the NNBSP in Ireland whereby screening for ADA-SCID was implemented in May 2022.

The incidence of SCID is noted to vary internationally, with the introduction of NBS screening for SCID previously cited as being associated with a general increase in the number of SCID cases detected.[8, 13, 25] Given the nature and severity of the condition, it is likely that such rises in incidence represent a detection of cases that would previously have died prior to being identified as SCID.[8, 13, 25] Irish data illustrates that there were 27 known cases of SCID diagnosed between 2005 and 2020, or 1 in 39,760 births, suggesting that, on average, there are approximately one to two cases of SCID diagnosed annually.[96] This rate is in line with those associated with conditions currently screened for within the NBBSP; as outlined in section 2.2.1, these range from 1 in 155,200 (maple syrup urine disease) to 1 in 2,300 (each of congenital hypothyroidism and cystic fibrosis).

As highlighted, there are at least 19 known genes that are associated with SCID.[2, 3] This gene panel is unlikely to be complete, as emphasised by the proportion of SCID

cases which meet the diagnostic criteria for SCID, but for whom the genotype remains unknown, with ongoing research in genomic sequencing uncovering novel mutations and genes associated with SCID on an ongoing basis.[7, 8] Furthermore, it is noted that discrepancies exist internationally in terms of the classification of genotypes for SCID. While X-linked SCID (that is, mutations in the IL2RG gene) retains a relative constant in terms of global incidence, proportions of autosomal-recessive-based SCID are variable.[7, 25] In particular, within the Irish population, a considerable proportion of SCID cases are associated with ADA mutations with a founder mutation previously noted in the Irish Traveller population.[6] As such, the comparative proportion of ADA-SCID cases in Ireland, relative to other countries, is high. It should be noted that further information relating to ethnicity were not considered within this chapter in the context of historical cases; however, such consideration may be warranted in the future given changing demography in Ireland.

In the absence of population-based screening, detection of SCID relies on risk-based detection at birth or clinical presentation. Population-based screening for ADA-SCID by MS/MS was implemented in Ireland in May 2022. It is important to consider what additional benefits may be offered by TREC-based screening programme over and above the current rate of identification of children with SCID through risk-based detection at birth and screening for ADA-SCID by MS/MS. Knowledge of a family history of SCID (or other risk factor) typically facilitates early surveillance-based detection of the condition in an infant, whereas detection by clinical presentation manifests in the form of infectious and or non-infectious presentations.[5, 25, 26]

Data from Ireland over a 15-year period indicates that of the 27 cases identified, 19 (70.1%) were diagnosed clinically.[96] Nine of the 19 cases diagnosed clinically were ADA-SCID and thus would likely have been detected had the current ADA-SCID screening programme been in place. Therefore, considering these historical Irish data of 27 cases, and excluding ADA-SCID cases and those identified on the basis of family history, 10 children (37.1% of all SCID cases) would potentially have been identified by TREC-based screening in the 15-year period from 2005 to 2020. However, proportions derived from these figures may represent an underestimate of the denominator (that is, the full number of children born with SCID), given the potential for early mortality and the small historical sample size.

Consistently, data suggest that the age of diagnosis for those identified through family history or screening is lower than the age at which children are diagnosed clinically. Consequently, a later age at diagnosis through clinical presentation is associated with a later age at definitive treatment, compared to those identified on the basis of family history or screening. While typically presenting asymptomatically at birth, SCID is associated with considerable morbidity and mortality; however, such

factors appear largely reliant on the presence or absence of infections and complications prior to definitive treatment.[82, 137] Early identification facilitates the implementation of measures to mitigate such potential harms. While age is frequently cited as a significant factor is the success of treatment, it appears that age serves largely as a proxy for the clinical condition of the child before treatment.[82, 137] Outcomes of HSCT (that is, the primary treatment for SCID) may be influenced by a myriad of factors including pre-transplant condition, infection status at the time of treatment, donor source, conditioning regimen, and the prevention of post-treatment complications such as GvHD. Within the limited Irish data presented, it is illustrated that the number of infections prior to diagnosis, prior to treatment, and actively at the time of treatment, alongside admissions to paediatric ICU, were higher in those diagnosed clinically compared to those identified on the basis of a family history.[96] Similarly, poorer outcomes in terms of survival to definitive treatment and overall survival were highlighted for those diagnosed clinically (albeit with low rates of mortality across the cohort as a whole). A detailed systematic review of the effect of early versus late HSCT on SCID outcomes is presented in chapter five.

In interpreting the information presented within this chapter, it is important to consider that the rarity of SCID means that studies describing SCID and assessing outcomes typically span long time periods and or include multiple locations; as such, the information presented may not accurately reflect outcomes for children born with SCID in Ireland at the present time. In this way, factors to bear in mind include the heterogeneity of the condition, advances in diagnostics, variance in the means used for detection, and advances in treatment regimens; these factors, which have varied over time and across jurisdictions, present challenges when considering the evidence-base for this condition as a whole and the applicability of international data to Ireland specifically. Such elements will be further considered in the remaining chapters of this report.

4. Systematic review of TREC-based newborn screening for SCID

Key points

- A systematic review of T-cell receptor excision circles (TREC)-based newborn screening for severe combined immunodeficiency (SCID) was undertaken. The primary outcome of interest was the test accuracy of TREC-based screening for SCID and for T-cell lymphopenias (TCL) generally (including SCID), as measured through rates of detection of these conditions.
    - Secondary outcomes included rates of retest (that is, of repeat TREC analysis being performed on the same DBS), repeat DBS requests, and rates of referral, alongside any additional measures of effectiveness reported, such as programme uptake rates and perceptions of the programme.
- In population-based screening, typically if the results of the initial test (that is, the index test) are normal, no further testing is performed as part of the screening programme. Therefore, no reference standard is available for the study population, and this limits the reporting of test accuracy measures. Therefore, the measures presented in this review are positive predictive value (PPV), rates of false positivity (for any TCL, including SCID), and documented missed cases.
- Twenty-seven articles were included in this review, which included 27 unique cohorts presented by 19 studies. Fifteen studies reported the outcomes of TREC-based screening in isolation, three reported outcomes of combined TREC and kappa-deleting recombination excision circles (KREC)-based screening, and one reported TREC in combination with an embedded next-generation sequencing (NGS) panel. To note, for the latter two study types, TREC results could not be isolated for reporting in the present review and will not be summarised in these key points.
- Across the cohorts reported within this review, there was notable heterogeneity in terms of the screening algorithms, test methodologies, and TREC cut-off values used. A number of studies further reported changes over the course of the study period to the TREC cut-off used for the included cohorts.
- Of the 15 studies examining TREC-based screening in isolation (including 15 population-based cohorts, four pilot cohorts, and three referral-based cohorts):

- Rates of retest (range 0.24% to 2.03%), repeat DBS requests (range 0.02% to 0.61%), and onward referrals (range 0.02% to 0.11%) varied across the included cohorts; however, the accompanying ranges associated with the rates indicate that these outcomes were generally low as a proportion of the total population screened.
- The PPV for SCID (excluding other TCL causes) ranged from 0.80% to 20.00% with no clear trend in terms of the different TREC cut-off values used.
- The PPV for all TCL (including SCID) ranged from 20.29% to 89.36%; seven studies reported a PPV of 70% or higher. Of note, one study that reported a PPV of 100% was considered an outlier as such a value is highly unusual in the context of population-based screening. Some consistency was noted in terms of lower TREC cut-offs generally having higher PPVs.
- As a percentage of the total population screened, the false positivity rate was less than or equal to 0.09% across the included cohorts (range 0.00% to 0.09%); this represents cases which were not found to have any form of TCL (including SCID), but were initially reported as a positive screen. As a percentage of those with an abnormal screen result, the false positivity rate for all TCL (including SCID) reported for the included cohorts ranged from 10.64% to 79.71%; with seven studies reporting 30% or lower. Of note, one study that reported a false positivity rate of 0% was considered an outlier as such a value is highly unusual in the context of population-based screening.
- A limited number of missed cases were reported across the included studies with three cases of delayed-onset leaky SCID and one case of combined immunodeficiency noted as having been missed. Given that the included studies typically did not follow participants up systematically, this is likely an under-representation of the true number of missed cases.
- The incidence rates of SCID and non-SCID TCL (excluding prematurity), per live births, were calculated for 13 population-based cohorts that had at least one year of data. The incidence of SCID ranged from 1 in 1,525 live births (within a population with a founder mutation for Artemis SCID) to 1 in 85,009 live births. The incidence of non-SCID TCL ranged from 1 in 2,139 to 1 in 25,017. The ratio of SCID to non-SCID TCLs detected ranged from 1:2 to 1:38.

- The cases of SCID reported were associated with a diversity of genetic mutations. A wide range of potential causes of non-SCID TCL were reported, including congenital syndromes (such as 22q11.2 Deletion Syndrome), secondary causes (such as congenital heart disease), and those which are idiopathic in nature (which may be transient or persistent).
    - Five studies provided sufficient detail of the proportional breakdown of the causes of non-SCID TCLs identified. On average, across the studies, 50% of the non-SCID TCLs occurred as part of congenital syndromes (that is, a group of signs or symptoms that occur together and collectively characterise an abnormal condition), 24% were secondary to other causes (for example, maternal immunosuppression), and 26% were idiopathic. Given the distribution of these causes, and as TCL is associated with the development of infections, it is plausible that a substantial proportion of non-SCID TCLs would present clinically (either due to syndromic signs and symptoms or on the basis of infection) in the absence of their detection through TREC-based screening for SCID
- The uptake rate of newborn screening for SCID was presented for two population-based cohorts and three pilot cohorts, with a notably high uptake (≥98%) reported for all but one pilot study which was undertaken within the Navajo Nation in the United States (61%).
- One pilot study conducted in The Netherlands investigated parent perceptions of newborn screening for SCID through surveys and interviews. The authors noted that the majority of parents expressed support for newborn screening for SCID. Among parents whose child had an abnormal screening test result, themes of anxiety and stress when receiving an abnormal screening result, alongside dissatisfaction with the communication of such results, were documented (notably, results were communicated by general practitioners, prior to referral to a specialist, as opposed to by a specialist in the first instance).

- The overall reporting of individual studies was associated with a number of limitations. These included incomplete reporting of laboratory processes and screening algorithms, non-reporting of participant numbers per TREC cut-off used, inadequate reporting in terms of operational measures, and poor descriptions of the underlying causes of TCL. A large proportion of the

evidence base stems from cohorts within the United States which may impact the overall applicability of the findings. Similarly, a degree of overlap and duplicate reporting was identified; however, a concerted effort has been made only to include unique populations.

- Overall, from the studies identified within this review, there is noted variability in the cut-offs, methods and screening algorithms in use when considering TREC-based screening for SCID. As a proportion of the total population screened, the overall false positivity rates for all TCLs (including SCID) is considered to be low; however, when considering SCID explicitly, false positivity rates are notably higher.

4.1 Introduction

As noted in section 2.4, the generally accepted method of newborn screening for SCID internationally is the quantification of TRECs.[5, 6, 13] TRECs are a DNA by-product of normal T-cell development, with their quantification providing a surrogate marker for newly-formed T-cells.[5, 13] The TREC copy number is readily quantified by qPCR using primers that typically amplify the joint of the δrec-ψJα TREC.[13, 24] Given the aetiology of SCID, depleted or absent TREC counts can be used to identify newborns with possible T-cell lymphopenia (TCL) who may require follow-up testing (to establish a diagnosis) following the screening test. However, as highlighted, TREC assays identify TCL more generally and are not necessarily specific to SCID.[25, 50] The use of TREC-based screening for SCID may therefore identify both newborns with SCID and those with non-SCID TCLs.

The purpose of this chapter is to describe a systematic review of TREC-based newborn screening for SCID.

4.1.1 Accuracy of screening tests

Importantly, as outlined previously, screening is distinct from diagnosis, and positive screening tests require onward referral for confirmatory testing and subsequent diagnosis.[15]

Within the context of a screening programme, the concept of further testing following a positive screening test, in order to establish a diagnosis, is hereafter referred to as confirmatory testing. Confirmatory testing may also rule out the presence of a condition, resulting in a 'false positive' result being returned.

An ideal screening test would be one which perfectly discriminates between people who have a particular condition from people who do not. However, in practice this typically does not occur, and instead, some people without the condition being

screened for will receive a test result saying the condition has been detected (termed a "false positive") and some people with the condition will receive a screening result saying the condition has not been detected (termed a "false negative").[15] In the context of false positives, these may occur for healthy individuals or it may be the case that a screening test detects a condition which, although not the target of interest specifically, may be clinically relevant to some extent and hence reflects an incidental finding.

This discriminatory ability of a screening test is measured through a variety of metrics relating to test accuracy. Test accuracy describes the ability of an "index test" (that is, the test being evaluated) to discriminate between those that have a target condition (for example, SCID) and those that do not. To determine test accuracy, the performance of the index test must be compared with that of a "reference standard" (that is, the best available method for determining the presence of the target condition). Metrics associated with test accuracy include sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV), as outlined in Table 4.1.[15]

Table 4.1 Overview of measures used to determine test accuracy

	Reference standard	
Index test result	**Condition present**	**Condition absent**
Positive	True positive (a)	False positive (b)
Negative	False negative (c)	True negative (d)

- **Sensitivity** describes the proportion of those with the condition that are correctly classified as positive by the index test.
  - Sensitivity = a / (a + c)
- **Specificity** describes the proportion of those without the condition that are correctly classified as negative by the index test.
  - Specificity = d / (b + d)
- **Positive predictive value** describes the probability that when a test result is positive, that the person truly has the condition
  - PPV = a / (a + b)
- **Negative predictive value (NPV)** describes the probability that if a person's test result is negative, that they truly do not have the condition
  - NPV = d / (c + d)

4.2 Methodology

A protocol detailing the methods undertaken in this review has been published previously (available here). The reporting of this systematic review adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria.[138]

4.2.1 Review question

The following review question was formulated according to the Population, Index test, Reference test, Diagnosis (PIRD) framework for test accuracy reviews (as shown in Table 4.2):[139]

- What is the test accuracy of TREC-based screening for SCID, using DBS samples from newborn infants, compared with flow cytometry, T-cell proliferation analysis, genetic testing and or subsequent clinical diagnosis?

While the primary research question relates to the accuracy of TREC-based screening for SCID, further performance measures were assessed. These include:

- programme uptake rates
- detection of non-SCID TCLs
- rate of requests, and uptake, of retests, repeat dried bloodspot (DBS), and referral
- parental perceptions of screening programmes for SCID.

Table 4.2 PIRD framework for systematic review

Population	Newborn infants
Index test	TREC assay using DBS
Reference standard	Flow cytometry, T-cell proliferation analysis, genetic testing, and or subsequent clinical diagnosis of SCID
Diagnosis of interest	SCID*

Key: DBS – dried blood spot; SCID – severe combined immunodeficiency; TREC – T cell receptor excision circles

*In keeping with the PIRD framework,[139] SCID is stated here as the 'diagnosis' of interest. However, it is important to note that TREC assays at birth identify infants with T-cell lymphopenia but do not provide a SCID diagnosis; confirmatory tests are required to provide a definitive diagnosis.

4.2.2 Types of studies

Cross-sectional studies, cohort studies, and large case-series were considered eligible for inclusion. Pilot studies (defined as screening offered to a subset of a

population, for example, a sample of maternity hospitals) and population-based studies (defined as screening offered to a population as a whole) were considered eligible. A preference was given to studies that reported clinical performance given their increased clinical utility compared with studies reporting analytical performance.[140, 141]

In the context of this review, studies of clinical performance refer to the application of a test to a population in an attempt to differentiate between those with and without a condition, while studies of analytical performance refer to those that assess accuracy in relation to known control cases and additional clinical samples, or those which seek to assess an appropriate threshold value only. Studies reporting analytical performance, which were identified during the review, are reported in Appendix 4.1 to this report for information.

4.2.3 Test of interest

As outlined in section 4.1.1, test accuracy describes the ability of an "index test" (that is, the test being evaluated) to discriminate between those that have a target condition (for example, SCID) and those that do not. To determine test accuracy, the performance of the index test must be compared with that of a "reference standard" (that is, the best available method for determining the presence of the target condition). The index test of interest to this review was any assay quantifying TRECs using DBS. As per the reported diagnostic guidelines for SCID, the reference standards for comparison were flow cytometry, T-cell proliferation analysis, genetic testing, and or subsequent clinical diagnosis.[21, 38, 39]

4.2.4 Participants of interest

Participants of interest were newborns partaking in newborn bloodspot screening (NBS) screening for SCID (with or without other NBS tests).

4.2.5 Outcomes of interest

Primary outcomes

The primary outcome of interest was the test accuracy of TREC-based screening for SCID and for TCLs generally (including SCID), as measured through rates of detection of these conditions. As outlined above, metrics associated with test accuracy traditionally include sensitivity, specificity, PPV, and NPV. However, to accurately measure sensitivity, specificity, and NPV, the index test and reference standard (in this case the confirmatory test used in the screening algorithm, most commonly flow cytometry) must be performed for all participants.

Given the nature of the studies included, if the initial TREC test is normal, no further testing is performed as part of the screening programme, with only abnormal results being referred for confirmatory diagnostic testing. Hence, in line with previous reviews undertaken,[50] only the PPV and rates of false positivity are presented within this review. To note, while other metrics of test accuracy could not be appropriately calculated, where a study presented instances of missed cases of SCID or other TCLs, this was documented.

Secondary outcomes

Where reported, additional outcomes of interest included operational and effectiveness measures. These included:

- Retest rate: the number of retests performed on initial DBS samples (typically defined as a re-punch of the original DBS card collected).
- Repeat DBS rate: the number of new DBS samples requested, alongside the uptake rate of same and any documented reasons for non-completion.
- Referral rate: the number of newborns referred for confirmatory testing on the basis of TREC results, alongside the uptake rate of same and any documented reasons for non-completion.
- SCID incidence: the number of SCID cases diagnosed per number of newborns screened in population-based studies with at least one year of data.
- Non-SCID TCL incidence: the number of non-SCID TCL diagnosed per number of newborns screened in population-based studies with at least one year of data (to note, prematurity is excluded from this calculation).
- Programme uptake rate: the number of individuals partaking in newborn screening relative to the number offered.
- Parental perceptions of screening programmes for SCID.

4.2.6 Exclusion criteria

The following exclusion criteria were applied:

- studies of analytical performance in which both clinical samples and controls (that is, known SCID cases) were assessed in combination, or where the study's aim was to establish an optimal cut-off only
- non-human studies

- studies that included fewer than five newborns
- studies that were not available in the English language
- editorials, commentary, review articles, pre-prints, letters, and conference abstracts
- studies published before 2010.

4.2.7 Search Strategy

Electronic searches were conducted on 1 November 2021 in Medline (EBSCO), Embase (OVID) and the Cochrane Library, supplemented by a grey literature search. Backward and forward citation searching of returned citations of relevance was also undertaken. The full search strategy is presented in the supporting protocol (available here).

4.2.8 Study selection and data extraction

Study selection

Returned citations from the collective search were added to Covidence for reference management prior to removal of duplicates. Title and abstract screening was performed by two reviewers independently, applying the predefined eligibility criteria, with discrepancies resolved by discussion. Full texts of relevant studies were retrieved and independently assessed by two reviewers for inclusion, with disagreements resolved by discussion and the involvement of a third reviewer where required. Reasons for exclusion following full-text review were summarised and documented.

Data extraction

A standardised data extraction template was developed using Microsoft Excel software and was piloted prior to the undertaking of the review. Data extraction was performed by one reviewer, with all data extraction cross-checked by a second reviewer and discrepancies resolved by consensus. Where required, authors were contacted for clarification relating to study populations and outcomes.

4.2.9 Data synthesis

Given the heterogeneity of the included studies, a meta-analysis was not deemed to be appropriate and a narrative overview of results is instead presented.

Primary outcomes

The primary outcomes of interest related to test accuracy of TREC-based screening for SCID, of which only PPV and false positivity could be calculated within this present review. These metrics are presented for SCID in isolation, and for TCLs generally (including SCID), based on the following calculations:

- Positive predictive value: the likelihood that when a test result is positive the person truly has the condition. Presented as a percentage:
    - PPV = [(newborns correctly identified as SCID and or other TCL) / (number with completed confirmatory testing)]*100
- False positivity: the number of newborns referred for confirmatory testing who were not found to have SCID or another TCL condition. Presented as a percentage:
    - False positivity = [(number of newborns with abnormal screens who subsequently have normal confirmatory testing)/(number with completed confirmatory testing)]*100

Preterm infants may have temporary low TREC levels. Where disaggregated data were available, estimates of false positivity excluded results from infants identified as preterm, with these counts considered as TCL.

Secondary outcomes

As outlined in section 4.2.5, secondary outcomes included calculation of rates of retest, repeat DBS, referral, SCID incidence, non-SCID incidence, and programme uptake.

4.2.10 Quality appraisal

No standard method was identified by this review for the appraisal of studies which lack a reference standard for all participants enrolled. Previous reviews have used modified versions of the Standards for Reporting of Diagnostic Accuracy (STARD) guidelines as a means to report the completeness of reporting of included studies.[50, 62] The Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool is considered the gold standard for the appraisal of quality of studies of diagnostic accuracy, but again necessitates the use of a reference standard applied to the study population as a whole.[142]

Given the intended uses of the STARD checklist and the QUADAS-2, and the significant modifications that would be required to facilitate appraisal within this present review, raising concerns about the overall validity of the tools, a decision

was taken to narratively synthesise the completeness of the reporting across the included studies, as opposed to applying a defined tool.

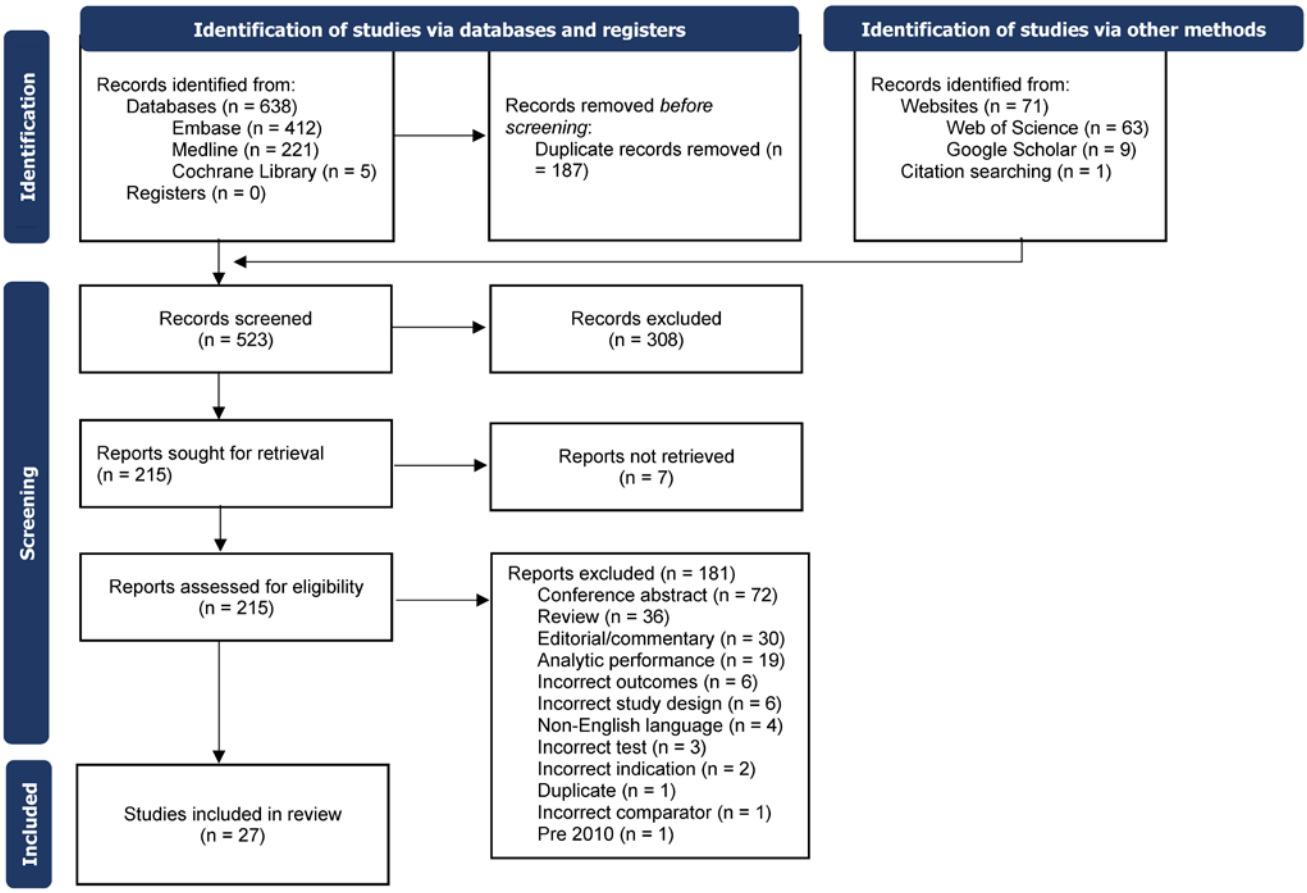
4.3 Results

4.3.1 Search results

The numbers of research articles screened, assessed for eligibility, and included in the present review (with reasons for exclusions) are presented in the PRISMA flow diagram of search results below (Figure 4.1). As shown, the collective search returned 710 citations. Following duplicate removal, the titles and abstracts of 523 citations were screened with 215 full-texts assessed for eligibility. Based on the defined exclusion criteria, 188 citations were excluded (Figure 4.1). Nineteen studies were deemed to report outcomes relevant to analytical performance as opposed to clinical performance, and were excluded from the main review; however, their details are documented in Appendix 4.1 for information.

Accordingly, 27 studies were included within the review.[54, 55, 64, 91, 104-109, 143-159] Of these, 19 studies,[55, 64, 91, 104-109, 145, 146, 148-152, 154, 156, 159] presented 27 unique cohorts. The remaining eight papers were found to represent duplications of populations included by primary studies within the review and hence were assessed for any additional information of relevance only.[54, 143, 145, 147, 153, 155, 157, 158] To note, one study included within the review described cohorts from 10 individual states (plus one cohort from the Navajo Nation) in the United States,[106] of which four were captured in more recent studies included within the review; as such, only information from the remaining seven cohorts were extracted for this study.[104, 105, 107, 109]

Figure 4.1 PRISMA flow diagram for review of TREC-based screening



4.3.2 Study characteristics

The characteristics of the included studies are presented in Table 4.3. Of the 19 studies presenting unique cohorts,[55, 64, 91, 104-109, 145, 146, 148-152, 154, 156, 159] eight were considered to be population-based cohorts (with one study presenting individual cohorts from seven US states),[55, 91, 104-106, 108, 109, 149] six were considered to be pilot cohorts,[145, 146, 148, 151, 152, 159] three were referral-based studies (where only the outcomes of those referred for confirmatory testing were reported),[64, 150, 154] and two reported both pilot and population-based cohorts as separate groups.[107, 156]

Fifteen studies reported the outcomes of TREC-based screening in isolation,[55, 64, 91, 104-109, 145, 146, 148-150, 154] three reported outcomes of combined TREC and kappa-deleting recombination excision circles (KREC)-based screening,[151, 152, 159] and one reported the outcomes of TREC in combination with an embedded next generation sequencing (NGS) panel (in this case, DNA sequencing tests to identify genes associated with primary immunodeficiency).[156] To note, for the latter two study types, results relating to TREC specifically could not be isolated for reporting in the present review.

Of the **population-based cohorts** for which TREC outcomes were reported in isolation, collectively, data from 5,997,843 infants were analysed (including data from 570 children who were not considered to be newborns, but were screened as part of immigration processes in one study).[55, 91, 104-109, 149] These cohorts were identified from Israel,[108] the Catalonian region of Spain,[91] Sweden,[55] and, within the United States, the states of California,[104] Wisconsin,[106, 149] Massachusetts,[105] Navajo Nation (Arizona and New Mexico),[107] Colorado,[106] Connecticut,[106] Delaware,[106] Michigan,[106] Mississippi,[106] Texas,[106] and New York.[109]

Of the **pilot cohorts** with TREC outcomes in isolation,[107, 145, 146, 148] data were reported for 439,301 newborns, with participants from France,[145] The Netherlands,[146] Taiwan,[148] and the Navajo Nation in the United States.[107] Of the three **referral-based studies** following TREC-based screening, the outcomes of 409 infants were reported from single centres in the states of Illinois and Missouri,[154] Wisconsin,[64] and New York.[150] Of the three studies including a **combined TREC and KREC analysis**,[151, 152, 159] all were considered to be pilot studies with 135,701 newborns screened across Sweden,[159] Turkey,[152] and the Polish-German trans-border area.[151] The one study including TREC analysis **combined with a NGS panel** reported results for a pilot study of 21,232 newborns in six selected hospitals in Norway,[156] followed by a population-wide cohort of 88,000 newborns.[156]

Within the French DEPISTREC study by Audrain et al.[145] described in the main results below, a subsequent economic analysis was completed in 2019.[157]

Table 4.3 Study characteristics

Study (year)	Country (region)	Population	Study duration	Total screened
TREC analysis: Population-based cohort studies				
Amatuni 2019[104] Additional reporting: Kwan 2013[153]	United States (California)	Newborns born in California.	15 August 2010 to 31 March 2017	3,252,156
Argudo-Ramírez 2021[91] Additional reporting: Argudo-Ramírez 2019[143] and Martin-Nalda 2019[155]	Spain (Catalonia)	Newborns born in Catalonia.	January 2017 to June 2020	222,857 (of which 220,706 analysed)
Cogley 2021[149]	United States (Wisconsin)	Newborns born in Wisconsin 24-48 hours after birth.	1 September 2018 to 31 March 2021	157,172
Göngrich 2021[55]	Sweden	Newborns across Sweden with DBS collected as soon as possible after 48 hours of age. Samples also collected from children immigrating to Sweden, who were between one month and two years old. Sample collected from back of the hand.	5 August 2019 to 4 August 2020	115,786: 115,216 newborns and 570 children aged 28 days to 2 years of age
Hale 2021[105]	United States (Massachusetts)	Newborns born in Massachusetts.	1 February 2009 to 31 January 2019	720,038
Kwan 2015[107]	United States (Navajo Nation: Arizona and New Mexico)	Newborns born in Navajo Nation maternity hospitals in Arizona and New Mexico.	February 2012 to July 2014	6,100

Study (year)	Country (region)	Population	Study duration	Total screened
Kwan 2014 - Colorado[106]	United States (Colorado)	All newborns screened by Colorado screening programme.	1 February 2012, to 31 March 2013	70,989
Kwan 2014 - Connecticut[106]	United States (Connecticut)	All newborns screened by Connecticut screening programme.	1 October 2011 to 1 May 2013	57,136
Kwan 2014 - Delaware[106]	United States (Delaware)	All newborns screened by Delaware screening programme.	6 July 2012 to 30 June 2013	11,202
Kwan 2014 - Michigan[106]	United States (Michigan)	All newborns screened by Michigan screening programme.	1 October 2011 to 31 March 2013	162,528
Kwan 2014 - Mississippi[106]	United States (Mississippi)	All newborns screened by Mississippi screening programme.	1 January 2012 to 31 December 2012	37,613
Kwan 2014 - Texas[106]	United States (Texas)	All newborns screened by Texas screening programme.	1 December 2012 to 31 May 2013	183,191
Kwan 2014 - Wisconsin[106] Additional reporting: Verbsky 2012[158]	United States (Wisconsin)	All newborns screened by Wisconsin screening programme	1 January 2008 to 31 December 2012	340,037
Rechavi 2017[108]	Israel	All newborns born across Israel.	1 October 2015 to 30 September 2016	188,162 with 177,277 included within analysis due to exclusions (including failed amplification of control gene)
Vogel 2014[109]	United States (New York)	All newborns born in New York State.	29 September 2010 to 28 September 2012	485,912
TREC analysis: Pilot cohort studies				

Study (year)	Country (region)	Population	Study duration	Total screened
Audrain 2018[145] Additional reporting: Audrain 2021[144] and Thomas 2019[157]	France (48 maternity hospitals)	Newborns tested three days after birth in 48 maternity hospitals.	January 2015 to March 2017	190,517
Blom 2021a[146] Additional reporting: Blom 2021b[147]	The Netherlands (Utrecht, Gelderland and Zuid-Holland)	Parents of all newborns born in three of the twelve provinces of The Netherlands were asked to participate in study (opt-out consent). Samples collected 72-168 hours after birth.	April 2018 to February 2020	140,593
Chien 2015[148]	China (One screening centre in Taiwan responsible for screening 35-37% of newborns in Taiwan)	Newborns in one screening centre.	1 May 2010 to 31 December 2011	106,391
Kwan 2015[107]	United States (Navajo Nation)	Newborns born at two Navajo Nation hospitals in Chinle and Tuba City, Arizona.	1 March 2009 to undefined	1,800
TREC analysis: Referral-based studies				
Gans 2020[150]	United States (New York)	Those referred to one centre (of a possible 10) for follow-up following abnormal TREC screening.	2010–2017	Referrals for 199 (187 completed)
Mantravadi 2021[154]	United States (Illinois and Missouri)	Those referred to one centre (of a possible three) for follow-up following abnormal TREC screening. Excluded premature patients	July 2014 to January 2018	Referrals for 154

Study (year)	Country (region)	Population	Study duration	Total screened
		if their positive screen normalized when repeated after 36 weeks corrected gestational age.		
Thorsten 2021[64]	United States (Wisconsin)	Those referred to one centre (of a possible two) for follow-up following abnormal TREC screening. Excluded premature infants.	1 January 2009 to 31 December 2018	Referrals for 68
Combined TREC and KREC analysis				
Gizewska 2020[151] – Pilot	Polish-German transborder area (West-Pomerania, Mecklenburg-Western Pomerania and part of Brandenburg)	Newborns from two centres in Germany and one in Poland.	24 October 2018 and 31 December 2019	44,287
Zetterstrom 2017[159] – Pilot Additional reporting: Barbaro 2017[54]	Sweden (Stockholm county)	All newborns born in Stockholm county.	15 November 2013 to 14 November 2016	89,462
Kutlug 2021[152] – Pilot	Turkey (two hospitals in Sumsun)	Newborns born in two hospitals with heel samples taken 48-72 hours after birth.	1 October 2015 to 31 December 2016	1,952
Combined TREC and NGS analysis				
Strand 2020[156] - Pilot	Norway (six selected hospitals)	Newborns from six hospitals with DBS collected 48-72 hours after birth.	22 September 2015 to 31 December 2017	21,232

Study (year)	Country (region)	Population	Study duration	Total screened
Strand 2020[156] - Population	Norway	Newborns across Norway with DBS collected 48-72 hours after birth.	January 2018 to August 2019	88,000

Key: DBS - dried bloodspot, KREC - kappa-deleting recombination excision circles, NGS - next generation sequencing, TREC - T-cell receptor excision circles.

4.3.3 Screening processes and algorithms

The screening processes and algorithms reported by the included studies are summarised in Appendix 4.2. A brief summary of the main components is outlined by study type below.

TREC-analysis in isolation

Twelve studies reported outcomes of TREC-based screening for 19 unique population-based and pilot cohorts.[55, 91, 104-109, 145, 146, 148, 149] Variability was noted in terms of the approach to TREC measurement and the cut-offs used across the included cohorts. The use of commercial kits for TREC analysis (EnLite™ or SPOT-it™) was reported for six cohorts,[55, 91, 104, 108, 145, 146] with the remaining reporting the use of locally developed assays or not providing this information. All cohorts analysed included the use of a control gene, with beta-actin being the most frequently cited across 12 cohorts,[55, 91, 104, 106-108, 145, 146] followed by RNaseP in six,[105, 106, 109, 148] and RPP30 in one.[149]

The majority of studies reported measurements of TRECs per µL of blood, while one reported TRECs per 3.2 mm punch (inferred as per 3µL of blood, as per van der Spek et al.[50]),[146] one reported TREC per well (of the well plate used to prepare samples for analysis),[55] and one study implemented a novel TREC measurement described as 'Multiple of the Median (MoM)', which is a measure of how far an individual test result deviates from the median.[149]

Six studies reported adjustments to the TREC cut-off value used over the course of the study period,[55, 91, 104, 108, 145, 146] with all but one lowering the cut-off.[146] The TREC cut-offs used varied widely across the included cohorts, with the lowest value, at which a retest was performed, being ≤10 copies/3.2mm punch (inferred as approximately ≤3.3 copies per µL) in a pilot study in the Netherlands,[146] and the highest value being <252 copies/µL in a population-based study in Massachusetts, albeit noting that these studies used different analytical methods.[105]

The use of repeat TREC testing, through additional punches of the same DBS, was reported in all but three of the 19 cohorts;[106, 148] of these three, two requested additional DBS samples in the case of initial abnormal results,[106, 148] and one did not report on repeat TREC testing.[106] The use of initial TREC measurement in isolation, followed by repeat testing with control gene amplification, was reported in five cohorts.[104, 106, 107] The use of a lower immediate referral threshold which overruled a repeat TREC analysis was reported in eight cohorts.[91, 104-107, 145] The request for an additional DBS sample if borderline or inconclusive results were obtained was used in six cohorts.[91, 106, 108, 109, 148] Prematurity, and or neonatal intensive care unit

(NICU) admission, was explicitly considered within 11 cohorts; among these, refinements to algorithms typically included a lower TREC cut-off or the request for a repeat DBS at corrected gestational age (as discussed in section 2.4.1).[91, 104-107, 109, 145, 146, 149] Repeat DBS requests for failed control gene amplification were outlined within the algorithms of 12 included cohorts.[55, 91, 106, 107, 109, 145, 146, 149]

In all cohorts, confirmatory testing, following a TREC result below the specified cut-off, involved flow cytometry. A number of studies further reported the use of additional tests, including T-cell proliferation assays and gene sequencing, to establish the diagnosis. As outlined in Appendix 4.2, variable thresholds were reported for the diagnosis of SCID.

Referral-based studies

Given the premise of the study type, the three referral-based studies provided limited information on the laboratory processes used prior to onward referral.[64, 150, 154] One study reported a TREC cut off of TREC <200 copies/µL,[150] one of TREC <250 copies/µL for one location and cycle threshold (Ct) >37 for a second (that is, the number of cycles of amplification of DNA required in the polymerase chain reaction (PCR) process in order to cross a defined threshold).[154] In comparison, one study reported varying cut-off values over the study period.[64] All three studies included the use of flow cytometry for confirmatory testing with detailed diagnostic criteria presented for SCID and non-SCID TCLs.

Combined TREC and KREC analysis

Of the three pilot studies reporting the use of combined TREC and KREC analysis, all three reported the use of beta-actin as a control gene, with two using commercial kits,[151, 152] and one using a local assay.[159] All three studies reported the use of repeat testing on the same DBS sample in the case of initial abnormal results, with two highlighting repeat DBS requests in the case of failed control gene amplification.[151, 159] One study reported both the use of repeat DBS samples for inconclusive results and the consideration of prematurity within their algorithm.[151] Following repeat testing, one study utilised cut-offs of <6 TREC copies/µL and or <4 KREC copies/µL,[151] one used <7 TREC copies/µl and or <7 KREC copies/µl,[152] and one reported a final cut-off of <10 TREC copies/3.2mm and or <6 KREC copies/3.2mm (inferred as <3.33/ µL and <2/µL, respectively) following ongoing refinement during the study period.[159] All three studies reported the use of flow cytometry for confirmatory testing.

Combined TREC and NGS analysis

One study within this review reported the use of a second-tier NGS panel integrated within a screening algorithm using TREC analysis for both pilot and population-based cohorts in Norway.[156] Beta-actin was reported as the control gene used with samples measuring <25 TRECs/μL (<15 TRECs/μL for preterm infants) on initial testing retested on the same DBS. On retest, samples from full-term infants with persisting abnormal TREC values underwent sequencing. DNA derived from DBS was tested using a SCID-specific gene panel that contained 255 primary immunodeficiency disease genes. Abnormal results were referred for immunological testing, as appropriate. Infants with no mutations identified by the panel had a second sample taken and if TRECs were still abnormal, they were also referred.

4.3.4 Rates of retests, repeat DBS, and referral

The rates of retests (that is, of repeat TREC analysis on the same DBS sample), repeat DBS (that is, of requests for additional DBS samples), referral (that is, onward referral for confirmatory testing) and completed confirmatory testing (that is, of those who completed follow-up) reported across the included studies are summarised in Table 4.4 below (excluding referral-based studies given their nature). It is important to note that the rates presented will be influenced by the previously described screening processes and algorithms presented by the individual studies.

TREC-analysis in isolation

Twelve studies reported outcomes of TREC-based screening for 19 unique population-based and pilot cohorts.[55, 91, 104-109, 145, 146, 148, 149] Five cohorts were reported with sufficient information to calculate retest rates,[55, 91, 105, 146, 149] nine cohorts for repeat DBS rates,[55, 91, 107-109, 145, 146, 148, 149] 11 cohorts for referral rates, and 18 for confirmatory testing.[107]

Retest rates ranged from 0.24% of the total population screened in one pilot study in the Netherlands,[146] to 2.03% in a population-based study in Catalonia.[91] Rates of repeat DBS requests ranged from 0.02% in one cohort in Sweden,[55] to 0.61% in a pilot cohort in the Navajo Nation.[107] For cohorts with sufficient information presented, successful completion of repeat DBS requests ranged from 74% to 100%.[55, 91, 107, 145, 146, 149] Of the cohorts reporting discrepancies between the numbers of repeat DBS requested versus completed, reasons included death prior to repeat sample being collected, loss to follow-up, and parental refusal.[55, 145, 146, 149]

As a percentage of the total population screened, the rate of referral ranged from 0.02% in cohorts in California, Catalonia, and a pilot cohort in Taiwan,[91, 104, 148] to 0.11% in New York and a pilot cohort of the Navajo Nation.[106, 109] The reported rate of those completing confirmatory testing ranged from 0.01% in Colorado and Mississippi,[106] to 0.14% in Texas.[106] Eleven cohorts were presented with sufficient

data for the rates of completion of confirmatory testing to be calculated (that is, proportion of those referred for confirmatory testing following an abnormal screening result who completed such testing).This rate ranged from 80% to 100% (excluding one study that reported two referrals only),[55, 91, 104, 105, 107-109, 145, 146, 148, 149] with reasons for non-completion including death prior to follow-up, loss to follow-up, normal TREC prior to confirmatory evaluation, ongoing investigation, and parental refusal.[105, 107, 109, 145]

Combined TREC and KREC analysis

Of the pilot studies including a combined TREC and KREC analysis, the retest rates were 0.72%,[151] 3.64%,[152] and 0.78% of the total individuals screened.[159] Of note, one study reported that of the 696 repeat tests, 595 were due to KREC results in isolation,[159] while a second reported 49 of 71 retests being as a result of abnormal KREC values.[152] Rates of repeat DBS requests were 0.13%,[151] 4.92%,[152] 0.02%,[159] with two studies reporting 100% completion and the remaining study excluding those for whom repeat DBS were requested.[152] Rates of referral were 0.02%,[151] 3.64%,[152] and 0.10%,[159] with confirmatory testing completed in all referred for the two studies which reported this outcome sufficiently.[151, 159]

Combined TREC and NGS analysis

Of the Norwegian cohorts assessed using combined TREC and NGS analysis, the rate of repeat tests for the pilot and population-based cohorts was 0.17% and 0.09%, respectively.[156] Repeat DBS requests were made for 0.01% of the total population-based cohort screened and completed for all but one participant, who was lost to follow-up. Sufficient information was not presented for either cohort in terms of rates of referral and confirmatory testing.

Table 4.4 Rates of retest, repeat DBS requests, referral, and confirmatory testing across included cohorts

Study (year)	Cut-off first TREC test	Cut-off repeat TREC tests	Total screened	Total repeat TREC (% screened)	Total requests repeat DBS (% screened)	Repeat DBS completed (% requested)	Total referred (% screened)	Confirmatory testing performed (% screened)
TREC analysis: Population-based cohort studies								
Amatuni 2019[104, 153]	*Initial:* <25 copies/µL* *Adjusted (first):* <22 copies/µL* *Adjusted (second):* <18 copies/µL*	*Initial:* <25 copies/µL *Adjusted (first):* <22 copies/µL *Adjusted (second):* <18 copies/µL	3,252,156	NR	NR	NR	562 (0.02%)	562 (0.02%)
Argudo-Ramírez 2021[91, 143, 155]	*Initial:* <34 copies/µL* *Adjusted:* <24 copies/µL*	<20 copies/µL	220,706	4489 (2.03%)	470 (0.21%)	470 (100%)	48 (0.02%)	48 (0.02%)
Cogley 2021[149]	TREC MoM value >1.079	TREC MoM value >1.079	157,172	821 (0.52%)	180 (0.11%)	153 (85%)	46 (0.03%)	46 (0.03%)
Göngrich 2021[55]	*Initial:* <15 copies/well *Adjusted:* <10 copies/well	≤6 copies/well	115,786	1,428 (1.23%)	27 (0.02%)	20 (74%)	73 (0.06%)	73 (0.06%)
Hale 2021[105]	<252 copies/µL*	<252 copies/µL	720,038	2,072 (0.29%)	NR	NR	237 (0.03%)	190 (0.03%)
Kwan 2015[107]	<40 copies/µL*	<25 copies/µL	6,100	NR	NR	NA	NR	NR
Kwan 2014 - Colorado[106]	<40 TREC/µL	<40 TREC/µL	70,989	NR	NR	NR	NR	10 (0.01%)

Study (year)	Cut-off first TREC test	Cut-off repeat TREC tests	Total screened	Total repeat TREC (% screened)	Total requests repeat DBS (% screened)	Repeat DBS completed (% requested)	Total referred (% screened)	Confirmatory testing performed (% screened)
Kwan 2014 - Connecticut[106]	≤30 TREC/μL*	≤30 TREC/μL	57,136	NR	NR	NR	NR	22 (0.04%)
Kwan 2014 - Delaware[106]	<27 TREC/μL*	<27 TREC/μL	11,202	NR	NR	NR	NR	9 (0.08%)
Kwan 2014 - Michigan[106]	≤11 TREC/μL*	NA	162,528	NA	NR	NR	NR	114 (0.07%)
Kwan 2014 - Mississippi[106]	≤25 TREC/μL	NA	37,613	NR	NR	NR	NR	5 (0.01%)
Kwan 2014 - Texas[106]	≤150TREC/μL*	≤150TREC/μL	183,191	NR	NR	NR	NR	249 (0.14%)
Kwan 2014 - Wisconsin[106, 158]	<30 TREC/μL	<30 TREC/μL	340,037	NR	NR	NR	NR	108 (0.03%)
Rechavi 2017[108]	*Initial:* <36 copies/ μL *Adjusted:* <23 copies/ μL	*Initial:* <36 copies/ μL *Adjusted:* <23 copies/ μL	177,277	NR	561 (0.32%)	NR	46 (0.03%)	46 (0.03%)
Vogel 2014[109]	<200 copies/μL	<125 copies/μL	485,912	NR	1,307 (0.27%)	NR	531 (0.11%)	478 (0.10%)
TREC analysis: Pilot cohort studies								
Audrain 2018[144, 145, 157]	*Initial:* <35 TREC copies/μL* *Adjusted:* <21 TREC copies/μL*	*Initial:* <21 TREC copies/μL *Adjusted:* <21 TREC copies/μL	190,517	NR	291 (0.15%)	238 (81.8%)	165 (0.09%)	140 (0.07%)
Blom 2021a[146, 147]	*Initial:* ≤ 6 copies/3.2mm	*Initial:* ≤ 6 copies/3.2mm	140,593	333 (0.24%)	54 (0.04%)	40 (74.0%)	47 (0.03%)	47 (0.03%)

Study (year)	Cut-off first TREC test	Cut-off repeat TREC tests	Total screened	Total repeat TREC (% screened)	Total requests repeat DBS (% screened)	Repeat DBS completed (% requested)	Total referred (% screened)	Confirmatory testing performed (% screened)
	Adjusted: ≤ 10 copies/3.2mm	*Adjusted:* ≤ 10 copies/3.2mm						
Chien 2015[148]	<40 TRECs/μL	NA	106,391	NA	432 (0.41%)	NR	24 (0.02%)	24 (0.02%)
Kwan 2015[107]	<33 copies/μL	<33 copies/μL	1,800	NR	11 (0.61%)	11 (100%)	2 (0.11%)	1 (0.06%)
Combined TREC and KREC analysis								
Gizewska 2020[151] – Pilot	TREC <6 copies/μL and or KREC <4 copies/μL	TREC <6 copies/μL and or KREC <4 copies/μL	44,287	321 (0.72%)	58 (0.13%)	58 (100%)	8 (0.02%)	8 (0.02%)
Kutlug 2021[152] – Pilot	TREC and or KREC <7 copies/μl	TREC and or KREC <7 copies/μl	1,952	71 (3.64%)	96 (4.92%)	Excluded	71 (3.64%)	36 (unclear due to exclusions)
Zetterstrom 2017[54, 159] – Pilot	TREC <25 copies/3.2 mm KREC <15 copies/3.2 mm	*Initial:* <15 TREC copies/3.2mm, <10 KREC copies/3.2mm *Adjusted (first):* <8 TREC copies/3.2mm, <4 KREC	89,462	696 (0.78%)	15 (0.02%)	15 (100%)	93 (0.10%)	86 (0.10%)

Study (year)	Cut-off first TREC test	Cut-off repeat TREC tests	Total screened	Total repeat TREC (% screened)	Total requests repeat DBS (% screened)	Repeat DBS completed (% requested)	Total referred (% screened)	Confirmatory testing performed (% screened)
		copies/3.2mm *Adjusted (second):* <10 TREC copies/3.2mm, <6 KREC copies/3.2mm						
Combined TREC and NGS analysis								
Strand 2020[156] - Pilot	<25 TRECs/μL	<25 TRECs/μL	21,232	37 (0.17%)	NR	12 (NR)	NR	NR
Strand 2020[156] - Population	<25 TRECs/μL	<25 TRECs/μL	88,000	81 (0.09%)	12 (0.01%)	11 (91.6%)	NR	NR

Key: KREC - kappa-deleting recombination excision circles, MoM - multiple of the median, NA - non-applicable, NGS - next generation sequencing, NR - not reported, TREC - T-cell receptor excision circles, μL - microliter. *specified lower values within study considered urgent positive associated with immediate referral (see appendix 4.2), ^excluded those with failed gene amplification. Note: results were calculated from counts provided by the studies included.

4.3.5 Accuracy of TREC-based newborn screening

On the basis of confirmatory testing performed, Table 4.5 below outlines:

- The rates of abnormal test results per population screened, which were confirmed to be truly abnormal on the basis of confirmatory testing (causes of abnormal results are classified as: SCID, atypical SCID, non-SCID TCL, preterm).
- The rate of false positive results for TCL (including SCID) as a percentage of all results referred for confirmatory testing due to a signal of abnormality (confirmed to be false on the basis of confirmatory testing).
- The rate of false positive results for TCL (including SCID) as a percentage of the population screened (confirmed to be false on the basis of confirmatory testing).
- PPV for SCID.
- PPV for TCL (including SCID).

These results are summarised by study type below.

TREC-analysis in isolation

Twelve studies reported outcomes of TREC-based screening for 19 unique population-based and pilot cohorts.[55, 91, 104-109, 145, 146, 148, 149] The rates of abnormal T-cell results from confirmatory testing, as a percentage of the total population screened, were less than or equal to 0.07% across all included cohorts (range 0.01% to 0.07%). In calculating the false positivity rate, two different denominators can be considered:

- the percentage of all those with abnormal screening test results for whom completed referrals for confirmatory testing took place (and for which at least two newborns were referred)
- the percentage of the total population screened.

Considering the former, the false positivity rate for all TCL (including SCID) ranged from 0.00% for a population-based cohort in Mississippi,[106] to 79.71% for a population-based cohort in New York.[109] Considering the latter (that is, the percentage of the total population screened), the false positivity rate was less than or equal to 0.09% across the included cohorts (range 0.00% to 0.09%).

To note, where reported, estimates of false positivity exclude results from infants identified as preterm; however, these counts are included within estimates for TCL. The potential causes of false positive results (for example, transient TCL) were typically not reported by the included studies.

The PPV for SCID excluding other TCL causes ranged from 0.80% for a population-based cohort in Texas,[106] to 20.0% for a population-based cohort in Mississippi.[106] For context, in a screening programme of 100,000 newborns screened, if 110 were identified as having an abnormal screen result, the number of infants that would truly have SCID, based on these estimates, would range from one to 22. As highlighted in Figure 4.2, with pragmatic cut-off groupings applied, the PPV was variable across the included studies with no clear trend in terms of the different TREC cut-off values used. It should be noted that the cut-offs used varied depending on the method of TREC measurement and algorithms in place; therefore, direct comparisons across studies are of limited value.

Of those studies with completed referrals for at least two newborns, the PPV for all TCL (including SCID) ranged from 20.29% for a population-based cohort in New York,[109] to 100% for a population-based cohort in Mississippi.[106] For context, in a screening programme of 100,000 newborns screened, if 110 were identified as having an abnormal screen result, the number of infants that would truly have TCL (including SCID), based on these estimates, would range from 22 to 110.

It should be noted that while no false positive cases were documented in Mississippi, and hence the PPV was documented to be 100%, this is an unusual finding when considering a population-based screening programme. The authors further provide a 95% confidence interval around this false positive rate estimate, which ranged from 0 to 45. As highlighted in Figure 4.3, with pragmatic cut-off groupings applied, the PPV across the studies was variable.

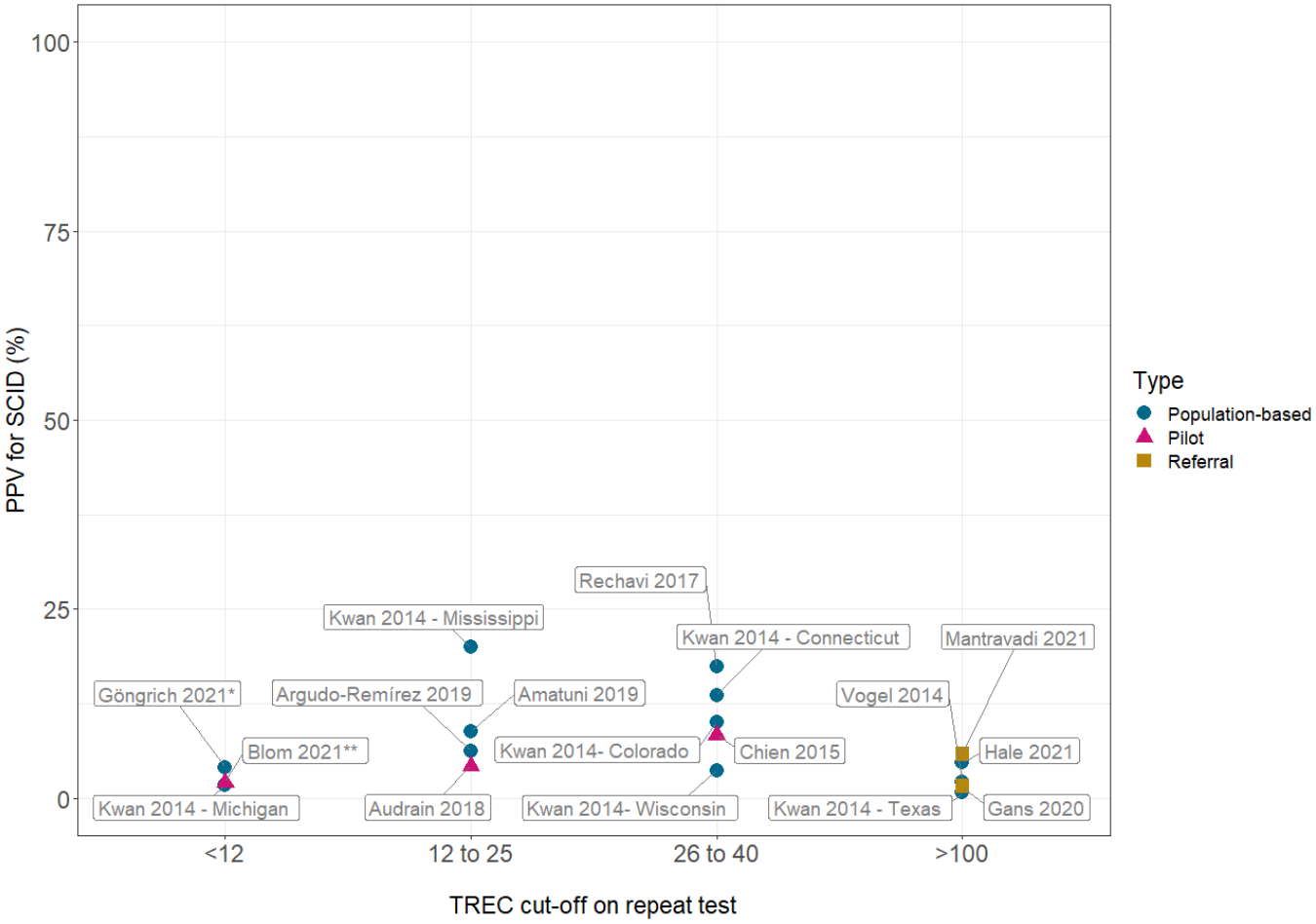
Some consistency was noted in terms of lower TREC cut-offs generally being associated with higher PPVs. However, there were notable exceptions to this trend; for example, a population-based cohort in Massachusetts with the highest TREC cut-off reported across all studies (<252 copies/µL) reported a PPV of 88.95%.[105] Again, it should be emphasised that such cut-offs vary depending on the method of TREC measurement and algorithms in place; therefore, direct comparisons across studies are of limited value.

Referral-based studies

Given the premise of the study type, data for the three referral-based studies were used to calculate false positivity for TCL (including SCID), PPV for SCID, and PPV for

TCL (including SCID) based on completed referrals only.[64, 150, 154] The false positivity rate (that is, the rate of false positives among those referred for confirmatory testing on the basis of an abnormal screen result) reported across the three studies was 71.12%,[150] 60.39%,[154] and 50.00%.[64] PPV for SCID was 1.59%,[150] 5.84%,[154] and 11.76%,[64] while PPV for TCL (including SCID) was 29.63%, 39.61%, and 50.00%.[64] As shown in Figures 4.2 and 4.3, the two studies which provided TREC cut-off information for their referral locations were on the higher end of the scale.

Figure 4.2 PPV for SCID across TREC cut-off groupings

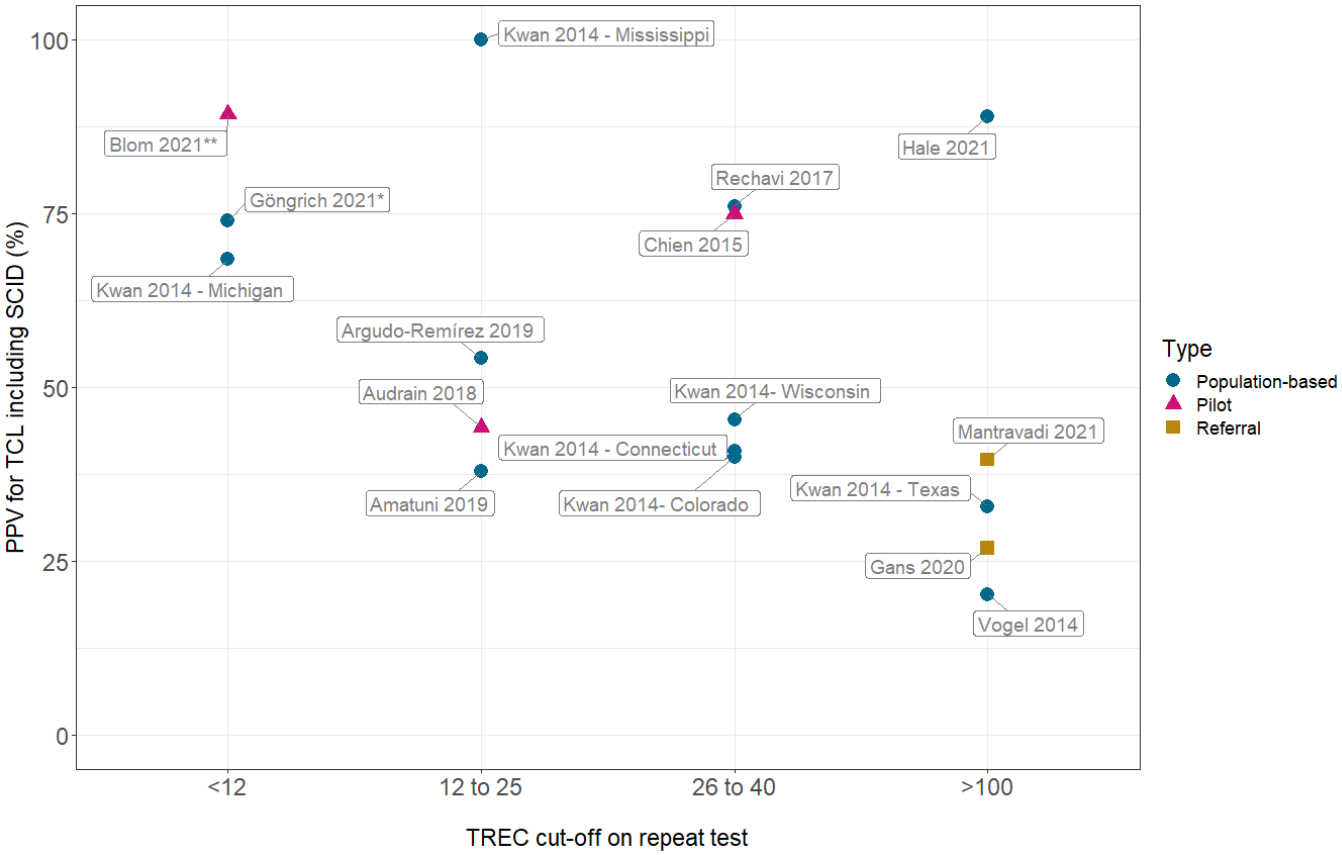


*TREC measurement in copies per well,

**TREC measurement in copies per 3.2mm

Note: Figure excludes Cogley et al.[149] due to Multiple of the Median TREC measurement. Figure is intended for illustrative purposes - cut-offs vary depending on the method of TREC measurement and algorithms in place; therefore, direct comparisons across studies are of limited value.

Figure 4.3 PPV for all TCL (including SCID) across TREC cut-off groupings



*TREC measurement in copies per well,

**TREC measurement in copies per 3.2mm

Note: Figure excludes Cogley et al.[149] due to Multiple of the Median TREC measurement. Figure is intended for illustrative purposes - cut-offs vary depending on the method of TREC measurement and algorithms in place; therefore, direct comparisons across studies are of limited value.

Combined TREC and KREC analysis

Of the three pilot studies reporting the use of combined TREC and KREC analysis, data relating to accuracy were sufficiently reported by two of the studies.[151, 159] The rates of false positivity for TCL (including SCID), on the basis of those referred due to an abnormal screen, were 12.50% and 29.07%. The two studies reported PPVs for SCID of 12.50% and 2.33%, and PPVs for TCL (including SCID) of 87.50% and 70.93%. Of note, the authors of one study in Sweden reported that the use of KREC increased the overall false positivity rate. Therefore, these measurements were not applied to a subsequent population-based screening programme.[55]

Combined TREC and NGS analysis

Insufficient information was presented for either the pilot or population-based cohorts to estimate accuracy measures for the single study assessing combined TREC and NGS analysis.[156]

Table 4.5 Accuracy of TREC screening for SCID and other TCL causes

Study (year)	Total screened	Completed referrals	Total abnormal TCL findings (% total screened)	SCID	Non-SCID TCL	Preterm	TCL false positives (% of those referred due to abnormal results)	TCL false positives (% of the total population screened)	PPV SCID	PPV SCID + TCL
TREC analysis: Population-based cohort studies										
Amatuni 2019[104, 153]	3,252,156	562	213 (0.01%)	50	130	33	349 (62.10%)	0.01%	8.90%	37.90%
Argudo-Ramírez 2021[91, 143, 155]	220,706	48	26 (0.01%)	3	21	2	22 (45.83%)	0.01%	6.25%	54.17%
Cogley 2021[149]	157,172	46	23 (0.01%)	1	22	NR	23 (50.0%)	0.01%	2.17%	50.00%
Göngrich 2021[55]	115,786	73	54 (0.05%)	3	28	23	19 (26.03%)	0.02%	4.11%	73.97%
Hale 2021[105]	720,038	190	169 (0.02%)	9	133	27	21 (11.05%)	0.00%	4.74%	88.95%
Kwan 2015[107]	6,100	NR	4 (0.07%)	4	0	0	NR	NE	NE	NE
Kwan 2014 - Colorado[106]	70,989	10	4 (0.01%)	1	3	0	6 (60.0%)	0.01%	10.00%	40.00%
Kwan 2014 - Connecticut[106]	57,136	22	9 (0.02%)	3	5	1	13 (59.09%)	0.02%	13.64%	40.91%
Kwan 2014 - Delaware[106]	11,202	9	4 (0.04%)	1	3	0	5 (55.56%)	0.04%	11.11%	44.44%
Kwan 2014 - Michigan[106]	162,528	114	78 (0.05%)	2	76	0	36 (31.58%)	0.02%	1.75%	68.42%
Kwan 2014 - Mississippi[106]	37,613	5	5 (0.01%)	1	3	1	0 (0.0%)	0.00%	20.00%	100.00 %

Study (year)	Total screened	Completed referrals	Total abnormal TCL findings (% total screened)	SCID	Non-SCID TCL	Preterm	TCL false positives (% of those referred due to abnormal results)	TCL false positives (% of the total population screened)	PPV SCID	PPV SCID + TCL
Kwan 2014 - Texas[106]	183,191	249	82 (0.04%)	2	71	9	167 (67.07%)	0.09%	0.80%	32.93%
Kwan 2014 - Wisconsin[106, 158]	340,037	108	49 (0.01%)	4	42	3	59 (54.63%)	0.02%	3.70%	45.37%
Rechavi 2017[108]	177,277	46	35 (0.02%)	8	18	9	11 (23.91%)	0.01%	17.39%	76.09%
Vogel 2014[109]	485,912	478	97 (0.02%)	10	87	NR	381 (79.71%)	0.08%	2.09%	20.29%
TREC analysis: Pilot cohort studies										
Audrain 2018[144, 145, 157]	190,517	140	62 (0.03%)	6	49	7	78 (55.71%)	0.04%	4.29%	44.29%
Blom 2021a[146, 147]	140,593	47	42 (0.03%)	1	41	0	5 (10.64%)	0.00%	2.13%	89.36%
Chien 2015[148]	106,391	24	18 (0.02%)	2	16	0	6 (25.0%)	0.01%	8.33%	75.00%
Kwan 2015[107]	1,800	1	1 (0.06%)	0	1	0	0 (0.0%)	0.00%	NE	100.00 %
TREC analysis: Referral-based studies										
Gans 2020[150]	NR	187	56 (NE)	3	53	NR	133 (71.12%)	NE	1.59%	29.63%
Mantravadi 2021[154]	NR	154	61(NE)	9	52	Excluded	93 (60.39%)	NE	5.84%	39.61%
Thorsten 2021[64]	NR	68	34 (NE)	8	26	Excluded	34 (50.0%)	NE	11.76%	50.00%
Combined TREC and KREC analysis										

Study (year)	Total screened	Completed referrals	Total abnormal TCL findings (% total screened)	SCID	Non-SCID TCL	Preterm	TCL false positives (% of those referred due to abnormal results)	TCL false positives (% of the total population screened)	PPV SCID	PPV SCID + TCL
Gizewska 2020[151] – Pilot	44,287	8	7 (0.02%)	1	5	1	1 (12.50%)	0.00%	12.50%	87.50%
Kutlug 2021[152] – Pilot	1,952	36	NR	0	3	15	NR	NR	NE	NE
Zetterstrom 2017[54, 159] – Pilot	89,462	86	61 (0.07%)	2	24	35	25 (29.07%)	0.03%	2.33%	70.93%
Combined TREC and NGS analysis										
Strand 2020[156] - Pilot	21,232	NR	24 (0.11%)	3	15	6	NR	NR	NE	NE
Strand 2020[156] - Population	88,000	NR	NR	3	NR	4	NR	NR	NE	NE

Key: KREC - kappa-deleting recombination excision circles, NE - non-estimable, NGS - next generation sequencing NR - not reported, TCL – T-cell lymphopenia, TREC - T-cell receptor excision circles
Note: results were calculated from counts provided by the studies included.

4.3.6 Documented missed cases

While a number of the studies included within this review documented that there were no known additional cases of SCID and or non-SCID TCL up to the time of writing, three studies presented missed cases which had been reported.[55, 104, 154] One study reported two cases of delayed-onset leaky SCID (gene not specified) with normal neonatal TREC screens, but who came to clinical attention at seven and 23 months of age in California.[104] One case of combined immunodeficiency (major histocompatibility complex (MHC) class II deficiency) was reported for a child in Sweden subsequent to a normal newborn SCID screen.[55] One infant with leaky SCID (IL2RG mutation) was reported, despite not being suspected following population-based newborn screening for SCID in a US cohort.[154]

4.3.7 Incidence of SCID and non-SCID TCL, based on confirmatory testing

The incidence of SCID and non-SCID TCL (excluding prematurity) per live births were calculated for 13 population-based cohorts with at least one year of data, as presented in Table 4.7.[55, 91, 104-109, 149] The lowest incidence of SCID was 1 in 85,009 births in Wisconsin,[149] while the highest incidence was 1 in 1,525 for the Navajo Nation.[107] Of note, due to a founder mutation, the incidence of Artemis SCID (DCLRE1C) is particularly high in this population.[107] The incidence of non-SCID TCL, identified by TREC- based screening, calculated for the included studies ranged from 1 in 25,017 births in California,[104] to 1 in 2,139 births in Michigan.[106] From the data provided by these studies, the ratio of SCID to non-SCID TCLs detected ranged from 1:2 to 1:38.

The documented SCID subtypes and TCL causes (excluding prematurity) are presented for each of the 27 individual cohorts included in this review in Appendix 4.3. A collective summary of the SCID subtypes and TCL causes documented is presented in Table 4.6. To note, these groupings are presented as per reporting within individual studies and may not align with European classifications. Five studies provided sufficient detail of the proportional breakdown of the causes of non-SCID TCLs identified.[104, 105, 108, 109, 143] On average, across the studies, 50% of the non-SCID TCLs occurred as part of congenital syndromes (that is, a group of signs or symptoms that occur together and collectively characterise an abnormal condition), 24% were secondary to other causes (for example, maternal immunosuppression), and 26% were idiopathic. Given the distribution of these causes, and as TCL is associated with the development of infections, it is plausible that a substantial proportion of non-SCID TCLs would present clinically (either due to syndromic signs and symptoms or on the basis of infection) in the absence of their detection through TREC-based screening for SCID.

Table 4.6 Incidence of SCID and non-SCID TCL per live births

Study (year)	Country (region)	SCID incidence	Non- SCID TCL incidence (excluding preterm)
Amatuni 2019[104, 153]	United States (California)	1 in 65,043	1 in 25,017
Argudo-Ramírez 2021[91, 143, 155]	Spain (Catalonia)	1 in 73,569	1 in 10,510
Göngrich 2021[55]	Sweden	1 in 38,500	1 in 4,135
Hale 2021[105]	United States (Massachusetts)	1 in 80,004	1 in 5,414
Kwan 2015[107]	United States (Navajo Nation: Arizona and New Mexico)*	1 in 1,525	NA
Kwan 2014[106]	United States (Colorado)	1 in 70,989	1 in 23,663
Kwan 2014[106]	United States (Connecticut)**	1 in 19,045	1 in 11,427
Kwan 2014[106]	United States (Michigan)	1 in 81,264	1 in 2,139
Kwan 2014[106]	United States (Mississippi)	1 in 37,613	1 in 12,538
Kwan 2014[106, 158]	United States (Wisconsin)	1 in 85,009	1 in 8,096
Rechavi 2017[108]	Israel	1 in 22,159	1 in 6,565
Vogel 2014[109]	United States (New York)	1 in 48,591	1 in 5,585

*Outlier consistent with founder mutation in this population, **Connecticut noted to have low numbers screened

Table 4.7 Reported SCID subtypes and non-SCID TCL causes

SCID subtypes	Non-SCID TCL
Typical SCID:	**Syndromes:**
IL2RG	22q.11.2 Deletion (DiGeorge)
ADA	Trisomy 21
RAG1	Trisomy 18
IL7R	Ataxia telangiectasia
JAK3	CHARGE syndrome
RAG1	Diabetic embryopathy
RAG2	CLOVES syndrome
PNP	EXTL3 deficiency
TTC7A	Fryns syndrome
CD3D	Nijmegen syndrome
DCLRE1C	Noonan syndrome
Unknown	Jacobsen syndrome
	RAC2 deficiency
Atypical SCID:	Cartilage-hair hypoplasia
ADA	17q12 duplication syndrome
RAG1	6p deletion syndrome
Omenn syndrome RAG1	Ring chromosome 17
JAK3	Alagille syndrome
IL7R	LIS1-associated lissencephaly
RAG2	Agammaglobulinemia
BCL11B	Spink5 Netherton syndrome
RMRP	Other combined immunodeficiency
DCLRE1	
TTC7A	**Secondary:**
Unknown	Congenital heart disease
	Hydrops
	Gastroschisis
	Chylothorax
	Maternal immunosuppression
	Third-space fluid leakage
	Intestinal atresia
	Meconium ileus
	Teratoma of the thymus
	Postnatal sepsis
	Juvenile myelomonocytic leukaemia
	Congenital diaphragmatic hernia
	Chylous ascites
	Severe asphyxia
	Congenital cytomegalovirus
	Congenital thoraco-cervical fibrosarcoma
	Idiopathic:
	Transient
	Persistent (mild or moderate)

4.3.8 Additional measures of effectiveness reported within studies

Uptake rates and perceptions of newborn screening for SCID

The uptake rate of newborn screening for SCID was presented for two population-based cohorts and three pilot cohorts.[55, 105, 107, 146, 159] Uptake rates for population-based cohorts were reported as 99.5% for Sweden,[55] and 98% for Massachusetts.[105] Uptake rates in pilot cohorts were 99.9% in Sweden,[159] 99.5% in the Netherlands,[146] and 61% in the Navajo Nation.[107] Of the lowest uptake rate presented for the Navajo Nation, the authors provided details of reasons for refusal. These included: 'mother not being interested in test'; 'believed baby looks healthy so test not required'; 'requested more time to consider'; 'voluntary so refused'; 'enrolling would be against traditional beliefs'; 'baby has had enough testing'; 'father or other family members refusal'; and 'the mother not being a member of the Navajo population'.[107]

The pilot study completed in the Netherlands provides a detailed overview of parent perceptions of newborn screening for SCID, examined through surveys and interviews.[146] The authors note that support for newborn screening for SCID was expressed by the majority of parents from a public health perspective in terms of believing that SCID was an important addition to the NBS programme (mean rating 4.3/5), and from a personal perspective in a desire for the condition to be detected as early as possible if their child had SCID (mean rating 4.2/5).

Reasons outlined for participating in NBS for SCID included; the potential health benefit for their child; to support scientific research; that no extra blood had to be drawn; that the disorder can be cured; and to help other children. Through statistical comparisons, the authors highlighted that parents who declined participation in newborn screening for SCID tended to have a more pessimistic attitude towards scientific research in general, and believed it to be of less importance that SCID be included in the NBS programme.

Of parents interviewed for whom their child had an abnormal result (n = 17), themes of anxiety and stress when receiving an abnormal screening result were documented; however, it was noted that, for the majority, their trust in the NBS programme had not been changed by this experience. These parents scored higher on a tool measuring the perception of vulnerability for the child compared with parents of newborns with a normal result.

Some parents of newborns, which were subsequently identified as false positives following confirmatory testing (n = 3), continued to perceive their newborn as more vulnerable. In terms of the communication of results, the parents of 12 newborns (out of 15 referred by a General Practitioner (GP)) had negative opinions of the

referral procedure, highlighting that they either received too little or incorrect information from the GP. Parents expressed a preference to be contacted by a paediatric immunologist directly rather than receiving initial counselling from the GP, so they could receive correct and clear information with the opportunity to ask questions.

4.3.9 Completeness of reporting

As noted within the methodology for this review, no standard method was identified for the quality appraisal of studies which lack a reference standard for all participants enrolled. In terms of the general completeness of reporting across the included studies, limitations noted within this review included:

- incomplete reporting of laboratory processes and screening algorithms
- non-reporting of participant numbers per TREC cut-off used where cut-offs were noted to vary within the study period
- inadequate reporting in terms of rates of retest, repeat DBS requests, referral and confirmatory evaluation
- poor descriptions of the underlying causes of TCL in abnormal cases.

4.4 Discussion

The purpose of this systematic review was to assess the accuracy of TREC-based newborn screening for SCID, with additional outcomes explored in terms of operational and effectiveness measures. The majority of the evidence identified stemmed from population-based and pilot cohorts partaking in TREC-based newborn screening, with a limited number of pilot studies assessing TREC-based screening in combination with KREC or NGS analysis. The included cohorts were notably heterogeneous in terms of the screening algorithms, test methodologies, and TREC cut-offs used. Rates of retest (range 0.24% to 2.03%), repeat DBS requests (range 0.02% to 0.61%), and onward referrals (range 0.02% to 0.11%) varied across the included cohorts that performed TREC analysis in isolation. While noting this variation, these rates were generally low as a proportion of the total population screened, as evident from the relatively narrow reporting ranges. The PPV for SCID across the included cohorts ranged from 0.80% to 20.0%, and for all TCLs (including SCID) from 20.29% to 89.36% (excluding an outlier of 100%).

Considering the latter, as a proportion of the total population screened, the false positivity rate was consistently less than 0.10% across all included cohorts. To note, these rates will further be influenced by the diagnostic criteria used, and the

potential causes of false positive results (for example, transient TCL) were generally not reported. Differential diagnoses for TCLs other than SCID included congenital syndromes, secondary, idiopathic, and prematurity causes. Given the nature of the studies included (that is, if the results of the initial TREC test(s) are normal, no further testing is performed), it was not possible to calculate false negative rates. A limited number of missed cases were documented within this review. However, given that all children screened did not undergo subsequent testing, this is likely an under-representation. Across the cohorts with sufficient information to estimate incidence of SCID and non-SCID TCLs, rates varied considerably. Limited information was presented in terms of the uptake rate, parental perceptions, and economic impact of such screening programmes.

The reported ranges for retests, resampling and onward-referral of screen-positive cases identified in this review were used to inform the resource and budget impact implications of implementing TREC-based screening for SCID (chapter seven). It is noted however that the testing method will need to be verified and appropriate TREC cut-off values established prior to implementation.

The variable PPVs noted for SCID and non-SCID TCLs, and those relating to operational measures (retest, repeat DBS, referrals) likely reflect the heterogeneity seen in terms of screening algorithms and TREC cut-off values used. These findings are in line with previous assessments undertaken in this area, including a 2015 systematic review,[50] a HTA in Spain,[137] and an evidence summary in the United Kingdom informing decision-making on the implementation of newborn screening for SCID.[62]

It is important to note that there was no clear linearity seen within this present review in terms of the TREC cut-offs and the PPVs reported, likely emphasising the influence of the screening method and algorithm as a whole. While some guidance may be provided by the existing literature, and manufacturer in the case of commercial kits, it is noted that the establishment and validation of appropriate cut-off values and algorithms will be required at the local level prior to the implementation of newborn screening programme for SCID.[8, 13, 24]

Considering individual patient TREC values, the authors of the 2015 systematic review suggest that a cut-off value of 25 TRECs/µl, with further consideration of preterm and NICU status, may be beneficial in terms of PPV for SCID. However, it is emphasised that the determination of such cut-off values should be made with consideration of the patient populations likely to benefit from identification beyond SCID specifically.[50] A number of population-based and pilot cohorts included within the present review were further noted to adjust the TREC cut-offs used during the

study period highlighting the potential need for ongoing refinement of this form of screening programme following its implementation.

Given the nature of the studies included within this review, limited information was presented with regards to missed cases; however, previous analytical studies have noted high rates of detection of known SCID cases used as controls.[160-162] The cases of SCID reported by the studies included within this review were associated with a diversity of genetic mutations and variability was further seen in terms of overall incidence. For some cohorts, such as the Navajo Nation,[107] founder mutations were cited as the rationale for particularly high incidences seen.

As mentioned, given the target of TREC analysis, this form of screening will detect TCL causes beyond SCID (as outlined by the associated PPVs). The inclusion of a component within a screening algorithm considering prematurity and or NICU status reflects the fact that preterm infants may typically present with low T-cell counts which begin to normalise with gestational age.[51] A comparative study of TREC counts in preterm and full-term infants in Wisconsin examined the relationship between TREC copy numbers and gestational age with the authors noting a 9.60% rise in TREC copy numbers per week of gestational age.[51] However, it is noted that preterm infants may also be diagnosed with SCID and, therefore, mechanisms to ensure these cases are still identified within a screening programme are important to include (such as the consideration of urgent positive screens with undetectable TREC levels).

With regards to non-SCID TCLs that may be identified as differential diagnoses in a newborn screening programme for SCID, a wide range of potential causes were reported by the studies in this review. These included congenital syndromes (such as 22q.11 deletion syndrome), secondary causes (such as congenital heart disease), and those which are idiopathic in nature (which may be transient or persistent). Given the range of other conditions that may be identified, it has been highlighted that consideration should be given to the infrastructure for their diagnosis, follow-up and management, should a decision to implement newborn screening for SCID be taken.[50, 62]

The clinical meaningfulness of the diversity of non-SCID TCLs that may be identified by TREC-based screening needs to be considered. Additionally, there may be some non-SCID TCLs identified which may present asymptomatically at birth, for which there is no curative treatment available, and for which the benefits of identification through screening may be less clear. An evaluation of the addition of SCID to the NBS programme in Quebec, published in May 2022, highlights ataxia telangiectasia as a particular example of note.[77] Ethical issues associated with these considerations are discussed in chapter nine.

A limited number of the included studies examined TREC analysis in combination with NGS or KREC. The use of embedded NGS based on a panel of primary immunodeficiency genes is a novel approach that was included in one study in this review. However such testing in the context of screening has been cited previously as potentially of limited benefit, given the ongoing emergence of new SCID mutations which would not be present in existing NGS panels.[8] The use of combined TREC and KREC analysis was used by three pilot studies in this review including 135,701 newborns screened (compared to 5,997,843 children for TREC in isolation). This form of screening is proposed to offer potential benefits in terms of the detection of delayed onset ADA-SCID and B-cell lymphopenias (BCL) specifically.[50] However, notably, the authors of one pilot study completed in Sweden, included within this review, reported that the use of KREC quantification increased the overall false positivity rate (particularly in terms of maternal immunosuppressive causes) and, as a result, KREC quantification was not applied in isolation in a subsequent population-based screening programme (that is, an infant must have evidence of TCL with or without BCL).[55]

No documented safety concerns with regards to physical harm were noted within the studies included in this review. As the process of sample collection is an extension of the already existing NBS test, it is anticipated that any additional harms would be associated with follow-up testing, for example in terms of physical and psychological impact, particularly when considering false positives; as discussed in chapter two, such follow-up testing initially would involve a clinical examination and blood draw to perform flow cytometry. One pilot study included in this review, which was completed in the Netherlands, provided a detailed overview of parent perceptions of newborn screening for SCID.[146] The authors noted that while the screening programme generally was well supported and associated with positive responses, interviews with parents of children with abnormal screening results presented with themes of anxiety and stress.

Additionally, there is a need to provide appropriate information to enable informed consent for screening to occur and to communicate abnormal screening results, with respect to both SCID and non-SCID TCLs, and the need to consider the patient and family experience (for example, the potential for anxiety) in the context of abnormal screen results. These will be discussed in chapter nine.

Further consideration will be needed at the verification stage in terms of the potential influence of the implementation of ADA-SCID screening (via MS/MS) on the accuracy measures outlined (for example, ADA-SCID screening may safeguard against false negatives that may occur in TREC-based screening for delayed-onset ADA-SCID, thereby helping to reduce the likelihood of cases being missed).

Limitations

The findings of this review should be interpreted in light of a number of potential limitations. As outlined, a large proportion of the evidence base stems from cohorts within the United States, which may impact on the overall applicability of findings. Similarly, when considering the United States cohorts, a degree of overlap and duplicate reporting was identified. However, a concerted effort has been made to only include unique populations within the present review.

Individual patient level data has not been considered within this review given the nature of the studies included. Such data may be presented within analytical based studies and may further inform the appropriateness of TREC cut-off values as has been described by a previous systematic review in the area.[50] However, such data may be of limited value when considering the local context and the implementation of a national level programme.

As noted, while a formal quality appraisal tool was not identified for the studies included in this review, the overall reporting was noted to be associated with a number of limitations, such as:

- incomplete reporting of laboratory processes and screening algorithms
- non-reporting of participant numbers per TREC cut-off used where cut-offs were noted to vary within the study period
- inadequate reporting in terms of rates of retest
- repeat DBS requests
- referral and confirmatory evaluation
- and poor descriptions of the underlying causes of TCL in abnormal cases.

Furthermore, the timing of sample collection was reported as less than 72 hours within a number of the included cohorts and may have contextual implications when comparing to the Irish setting (in which samples are collected in the first 72 to 120 hours of life).

Lastly, given the nature of the screening programme under consideration, whereby infants with normal screening results are not followed up systematically, limited information can be garnered in terms of additional measures of test accuracy such as sensitivity, specificity, or negative predictive value. Known missed cases have been documented where reported by individual studies, but this has limitations in terms of the completeness of reporting.

4.5 Conclusion

The findings of this chapter illustrate that considerable heterogeneity exists within the literature with regards to the screening algorithms and TREC cut-offs used for newborn screening for SCID. This heterogeneity translates to variability in the outcomes reported including those which relate to operational measures (such as rates of retests, repeat DBS, and referrals) and those that relate to test accuracy (such as PPV).

As a proportion of the total population screened, the overall false positivity rates when considering all TCLs are generally low; however, when considering SCID explicitly, false positivity rates are considerably higher. Differential diagnoses for other TCLs identified through TREC-based newborn screening include congenital syndromes, secondary, idiopathic, and prematurity causes. Across the cohorts with sufficient information to estimate incidence of SCID and non-SCID TCLs, rates varied considerably across the locations included.

5. Systematic review of early versus late diagnosis and or HSCT

Key points

- This chapter reports the findings of a systematic review of the potential clinical benefits associated with early diagnosis and or haematopoietic stem cell transplantation (HSCT) compared with late diagnosis and or HSCT. Primary outcomes of interest were safety and survival associated with early diagnosis and or HSCT compared with late diagnosis and or HSCT in those diagnosed with severe combined immunodeficiency (SCID). Secondary outcomes of interest included immune reconstitution and need for repeat HSCT or stem cell boosts.
- Fifteen publications, presenting data on 13 unique cohorts, were included in the systematic review. Apart from one prospective cohort study, all were retrospective cohort studies. Only two studies stratified participants into two independent groups and specifically comparing based on whether or not the infant received an early SCID diagnosis and or access to HSCT. The remaining studies considered the potential effect of early diagnosis and or treatment within single cohorts, as part of a broader analysis of a wide range of factors that could have impacted clinical outcomes.
    - All included studies reported results for survival outcomes. No safety data associated with adverse events (for example, procedural based events or complications) relating specifically to early versus late HSCT for the treatment of SCID were identified within this review.
- Across all of the included studies, there was noted heterogeneity in terms of the descriptions of ‘early’ versus ‘late’ diagnosis and or HSCT:
    - Four studies considered early versus late diagnosis. Two of these studies examined the impact of early diagnosis, with ‘early’ described as diagnosis antenatally or at birth, and ‘late’ described as diagnosis after birth (with one of these studies comparing siblings born with SCID). The remaining two studies compared those identified on the basis of family history or NBS with those diagnosed clinically, as well as comparing patients who received HSCT before or after 3.5 months of life.
    - Seven studies compared receipt of HSCT before or after 3.5 months of life, with three of these studies additionally exploring the interaction between age

and infection status. Infection status was considered in terms of 'active infection', 'resolved infection', or 'no infection'.

- Four studies compared age at receipt of HSCT based on different age cut-off definitions, with one comparing receipt of HSCT within or beyond 28 days of life, one within or beyond four months of life, and two within or beyond six months of life.

- Overall, 12 of the 13 independent studies provided evidence to suggest that early diagnosis and or HSCT led to improved survival outcomes compared with late diagnosis and or HSCT:
  - Three out of four studies which considered early versus late diagnosis showed improved outcomes in favour of earlier diagnosis.
    - The fourth study did not observe a significant difference in outcomes in terms of early versus late diagnosis, but also investigated the effect of age at HSCT and observed a significant effect for this comparison.
  - Ten out of 11 studies which included a comparison based on age at HSCT indicated higher survival in those receiving HSCT at an earlier age.
    - The eleventh study, while not finding a significant difference in terms of age at HSCT, did find a significant impact of the presence of pre-transplant infections (that is, those with pre-existing infections at the time of HSCT had poorer outcomes compared with those who did not).
- Eight studies reported the effect of pre-HSCT infections on survival outcomes; all observed that the presence of infections prior to HSCT negatively impacted overall survival. Further scrutiny of study findings suggests that differences in outcomes reported for early versus late HSCT may be a proxy for infection status prior to and up to the point of HSCT.
  - Studies consistently found that infections prior to HSCT negatively impacted overall survival.
  - Three studies included comparisons of age at HSCT (all using 3.5 months of life as the cut off) combined with infection status. Each study noted that, in the absence of infection, similar survival rates were observed in those receiving HSCT before and after 3.5 months. However, among infants with active infections at the time of transplant, higher survival rates were

observed in those receiving HSCT in the first 3.5 months compared to HSCT beyond 3.5 months of life.

- Improved outcomes in infants diagnosed with SCID or in receipt of HSCT at a relatively earlier age might be explained by the lower risk of complications due to infection; such lower risk is likely in turn related to the opportunity to institute infection prevention and control measures, prophylactic antibiotics and immunoglobulin replacement therapy at an earlier time.
- Given the rarity of SCID, many of the studies included clinical data from across several decades in their analysis. During this time, there have been improvements in supportive care and transplantation-related techniques (such as the available conditioning regimens and graft-versus-host disease (GvHD) prophylaxis). Accordingly, eight studies conducted sub-cohort analyses to investigate whether the time period in which transplantation was conducted translated into better outcomes for patients with SCID; five of these studies found that survival outcomes improved over time. It was not clear whether these improvements over time varied differentially across patients with 'early' versus 'late' diagnosis and or HSCT.
- Considering secondary outcomes included in this review:
    - One study included specific consideration of neurological outcomes. Diagnosis on the basis of family history or NBS (versus clinical diagnosis), and treatment with HSCT before 3.5 months of life, were each individually associated with better neurological outcomes. The method of diagnosis (family history or NBS, versus clinical) was highly correlated with infection status, with this being the only factor to continue to show a significant association with neurological outcomes in a multivariable analysis.
    - Three studies examined the need for repeat HSCT treatment, with all noting lower rates of repeat treatment in those who received earlier HSCT.
    - Variable results were shown in terms of the impact of age of HSCT on outcomes relating to immune reconstitution.
    - Two studies reported on differences in growth percentiles between patients with SCID who received HSCT before or after the first 3.5 months of life. A smaller proportion of the children who underwent early HSCT were below the third percentile for height and weight.
- The evidence base addressing this question is derived from observational studies that were primarily informed by retrospective review across multiple international settings, and across several decades. Furthermore, the studies identified by this

review were not formally designed to establish causality for the relationship between early versus late diagnosis, and or HSCT, and outcomes such as survival. However, these limitations reflect challenges in research related to rare diseases generally. Nonetheless, the evidence consistently suggests that earlier diagnosis and or HSCT is associated with improved clinical outcomes and survival for children with SCID.

5.1 Introduction

Haematopoietic stem cell transplantation (HSCT) is the primary treatment option for children diagnosed with SCID.[163] From a treatment perspective, the main advantage arising from the introduction of newborn screening would be the potential for earlier diagnosis and definitive treatment of infants with SCID with a view to achieving immune reconstitution and reducing the occurrence of adverse events such as severe infections.

This chapter, framed in this context, describes a systematic review undertaken to assess the potential clinical benefits associated with early diagnosis and or HSCT compared with late diagnosis and or HSCT.

5.2 Methods

A systematic review was undertaken to identify and assess the current international evidence of the clinical benefits and safety of early diagnosis and or HSCT compared with late diagnosis and or HSCT in children with SCID.

A protocol detailing the methods undertaken has been published previously (available here). The reporting of this systematic review adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria.[138]

5.2.1 Review question

The original review question, documented within the protocol, described early versus late HSCT in the context of the means of identification (that is, early being through NBS or family history, and late being clinical diagnosis following symptomatic presentation). However, on examination of the literature returned from the systematic search, this level of categorisation resulted in limited data; only three of the 12 studies identified used a categorisation based on means or age of diagnosis.

The remaining studies compared groups based on when the infant underwent transplantation, with cut-offs of 28 days, 3.5 months, four months, and six months reported. Therefore the definitions were reframed to include such groupings (including by age at diagnosis and or treatment). These definitions used were in line

with those used in previous assessments.[82, 137] The updated review question, formulated according to the Population, Intervention, Comparator, Outcomes and Study design (PICOS) framework (as shown in Table 5.1), was as follows:

What is the clinical effectiveness and safety of early compared with late diagnosis and or receipt of HSCT, as described by individual studies, in those diagnosed with SCID?

While the primary research question related to the clinical effectiveness and safety of early compared with late diagnosis or HSCT, other potential contributory or confounding factors and mediators were also assessed in this review.

Table 5.1 PICOS framework for systematic review

Population	Infants or children with SCID
Intervention	Early diagnosis or HSCT
Comparator	Late diagnosis or HSCT, or no treatment*
Outcomes	▪ Survival ▪ Incidence of adverse events associated with early HSCT ▪ Immune reconstitution ▪ Need for repeat HSCT or stem cell boosts ▪ Any other cognitive, behavioural and neurological outcomes
Study design	Retrospective or prospective cohort studies or analyses
Exclusion criteria	Non-human studies, case reports or series, papers not available in English, letters, editorials, commentaries, preprints, conference abstracts and studies published pre-2000.**

Key: HSCT – haematopoietic stem cell transplant, Ig – immunoglobulin; SCID – severe combined immunodeficiency

* No treatment means no definitive treatment for the purpose of achieving immune reconstitution.

** Scoping for this review indicated that over 90% of studies examined in previous reviews were published from the year 2000 onwards.[119, 164, 165] However, one study published in 1999 was included in the current systematic review because it was linked to two further studies published after 2000.[166-168]

5.2.2 Types of studies

Studies that were eligible for inclusion were retrospective and prospective cohort studies, in which the clinical outcomes of patients with SCID with an early diagnosis or treatment (HSCT) were compared with those that received a late diagnosis or treatment (HSCT).

5.2.3 Population of interest

The population of interest was infants or children with SCID.

5.2.4 Intervention of interest

The intervention of interest was early diagnosis and or HSCT as described by the included studies.

5.2.5 Comparator of interest

The comparator of interest was late diagnosis and or HSCT, as described by the included studies, or no treatment.

5.2.6 Outcomes of interest

Primary outcomes

The primary outcomes were safety and survival associated with early compared with late HSCT in those diagnosed with SCID. These outcomes included the change in survival or harms (adverse events) associated with early versus late HSCT.

Secondary outcomes

Where reported, additional outcomes of interest included immune reconstitution, and need for repeat HSCT or stem cell boosts.

5.2.7 Exclusion criteria

The following exclusion criteria were applied:

- non-human studies
- case reports or series
- papers not available in English
- letters, editorials, commentaries, preprints, and conference abstracts
- studies published pre-2000.

5.2.8 Search methods

Electronic searches were conducted in Medline (EBSCO), Embase (OVID), the Cochrane Library, Web of Science and Google Scholar between 2 and 3 November 2021. Forward citation searching and searching of the reference lists of included studies was also undertaken. The full search strategy is presented in the supporting protocol.

5.2.9 Study selection and data extraction

Study selection

Returned citations from the collective search were added to Covidence for reference management prior to duplicate removal. Title and abstract screening was performed by two reviewers independently applying the predefined eligibility criteria, with discrepancies resolved by discussion. Full-texts of relevant studies were retrieved and independently assessed by two reviewers for inclusion, with disagreements resolved by discussion and the involvement of a third reviewer where required. Reasons for exclusion following full-text review were summarised and documented.

Data extraction and management

A standardised data extraction template was developed using Microsoft Excel software and piloted prior to the undertaking of the review. Data extraction was performed by one reviewer, with all data extraction cross-checked by a second reviewer and discrepancies resolved by consensus.

5.2.10 Data synthesis

Given the high level of heterogeneity observed between the included studies (for example, with respect to statistical analysis and outcomes presented), a meta-analysis was not considered appropriate. Therefore, a narrative synthesis was undertaken.

5.2.11 Quality Appraisal

Each study was assessed by one reviewer, with the assessment cross-checked by a second reviewer. The National Heart, Lung and Blood Institute (NIH) quality assessment tool for observational cohort and cross-sectional studies was used to appraise the included studies.[169]

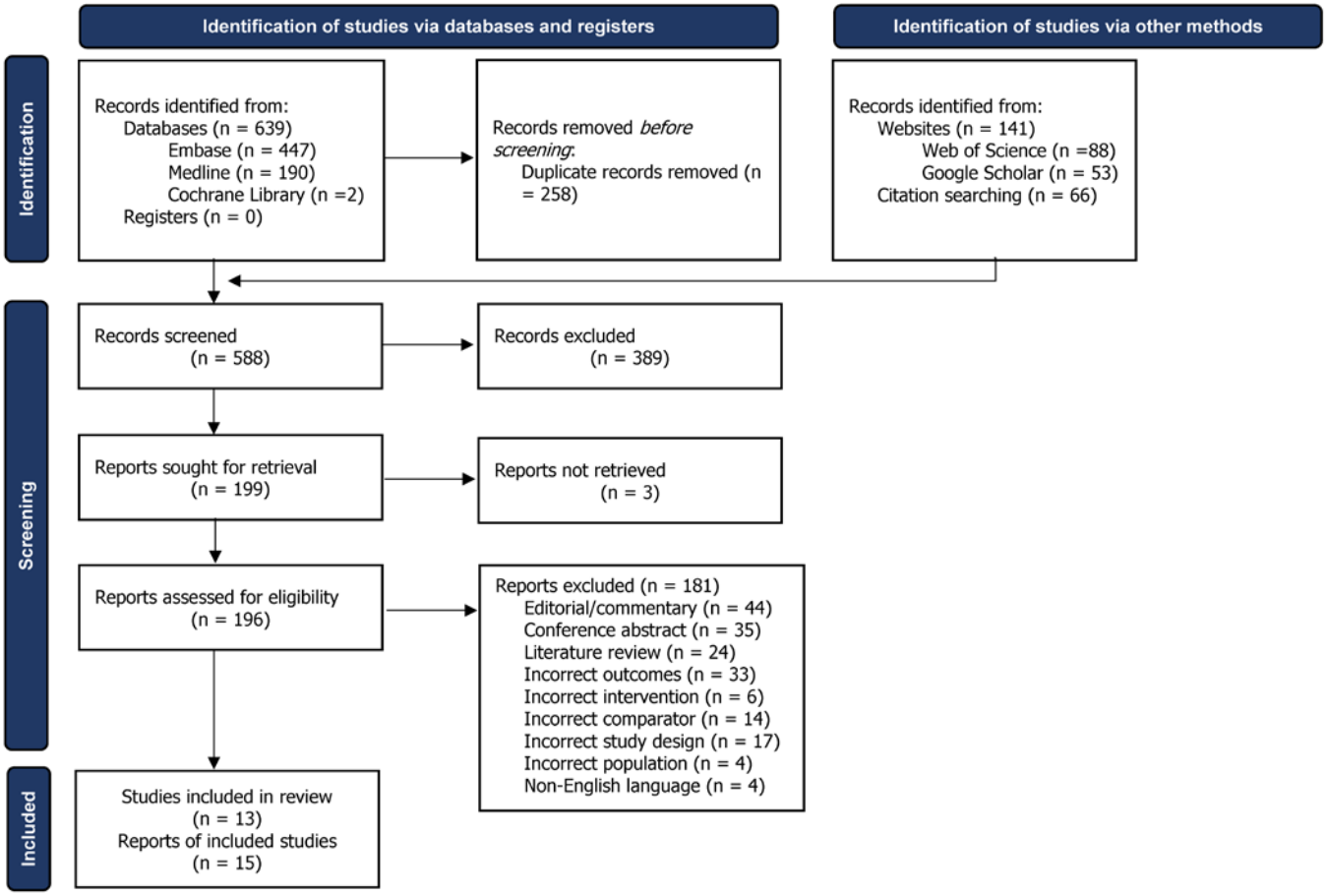
5.3 Results

5.3.1 Search results

The PRISMA flow diagram, outlining the flow of information during the systematic review process, is presented in Figure 5.1. Overall, a total of 846 citations were retrieved from the literature search. Of these, 258 were removed as duplicate citations. A further 389 were excluded following title and abstract screening. After completion of full-text review, 15 publications were identified that met the systematic review's eligibility criteria and were included in the synthesis.[118, 121, 122, 131, 133, 136, 166-168, 170-174] Three of the papers were linked updates (that is, the papers

were based on the same cohort with inclusion of more patients and longer follow-up times in updated versions) published between 1999 and 2011.[166-168] Therefore, 13 independent studies were included in the synthesis overall.

Figure 5.1 PRISMA flow diagram for systematic review



Key: n – number of studies, PRISMA – Preferred Reporting Items for Systematic Review and Meta-Analysis

5.3.2 Study characteristics

Overview

Characteristics of the included studies, published between 1999 and 2021, are presented in detail in Tables 5.2 to 5.3 and in Appendix 5.1. Twelve of the 13 independent studies were retrospective cohort studies (that is, the data were collected and analysed using existing records of infants with SCID who received a HSCT); one study reporting data from multiple tertiary centres in Canada and the US, was prospective in nature (that is, participants were enrolled when it was planned that the infant with SCID would receive a HSCT).[122] Overall, eight studies were based on clinical data from Canada and the US,[118, 121, 122, 133, 166-168, 171, 173, 174]

three were based on data from multiple centres across Europe,[136, 172, 175] one was from the UK,[170] and one was from Japan.[131]

Types of studies

Overall, there were two comparative studies, published in 2009 and 2011, in which study participants were stratified into two independent groups and compared based on whether or not the infant received an early SCID diagnosis and or access to HSCT.[133, 170, 173] The other 11 studies, published between 1999 and 2021, were non-comparative for the outcome of interest central to the present review (that is, they did not focus specifically on early versus late diagnosis and or HSCT) and considered the potential effect of early diagnosis and or treatment amongst a broad range of factors that could have impacted clinical outcomes (for example, age, infection status, use of conditioning, donor source and type within single cohorts).[118, 121, 122, 131, 136, 166-168, 171, 172]

Study setting

Three of the 12 independent retrospective cohort studies were based on chart reviews following cohorts of patients with SCID that received a HSCT in the same tertiary centre (Duke University Medical Center, North Carolina) between 1982 and 2010.[133, 166-168, 173] Another three of the 12 independent retrospective cohort studies were based on data from the Stem Cell Transplant in Primary Immune Deficiency in Europe (SCETIDE) registry of patients with SCID that underwent HSCT in centres across Europe between 1968 and 2014.[136, 172, 175] While all three studies included patients from the SCETIDE database, the 2003 study reported outcomes only for patients receiving transplantations from human leukocyte antigen (HLA)-identical donors,[175] the 2010 study reported outcomes for all patients with SCID,[172] and the 2021 study reported outcomes for a more recent cohort of patients.[136] One retrospective cohort study was informed by a survey of the parents of children with SCID in the US that were in the Immune Deficiency Foundation patient database, subscribers of the SCID Forum database, or enrolled as members of the SCID Angels for Life Foundation.[171]

Another US-based retrospective study, based on data from 1990 to 2016, included children with SCID who underwent HSCT at a single centre in California[174] The remaining four retrospective studies included data from patients with SCID that received HSCT in multiple centres across Japan, the US, Canada, and the UK at different time intervals between 1974 and 2016.[118, 121, 131, 170] The prospective study was based on data from Canada and the US between 2010 and 2014.[122]

Sample size and duration of follow-up

Overall, study sample sizes ranged from 75 to 699 patients with SCID. Eight independent studies reported the median length of follow-up,[122, 131, 133, 136, 166-168, 172, 174, 175] which ranged from a median of one year to a median of 10 years across all studies; within studies, the length of follow-up ranged from 1 day to 28.5 years. Four studies did not report the length of follow-up.[118, 121, 170, 171]

Patient demographics

The characteristics of study participants were often poorly reported. The sex of study participants was reported in eight studies; the majority of participants were male.[118, 121, 122, 131, 133, 136, 168, 173, 174] The ethnicity of study participants was reported in five studies; of those reported, the majority of participants were white.[121, 122, 133, 168, 173] The SCID subtypes or genotypes of study participants were reported in all 13 studies; overall, X-linked deficiencies were most commonly reported (IL2RG) followed by ADA deficiency. The criteria used to provide a diagnosis of SCID were reported in nine studies, with use of criteria from the WHO or IUIS most often reported.[121, 122, 131, 136, 166-168, 171, 172, 174, 175]

Twelve of 13 studies reported the median age at diagnosis and or HSCT.[118, 121, 122, 131, 136, 166-168, 170-175] The median age at diagnosis reported across studies ranged from 0 days (study range: 0 to 29 days) to 239 days (study range: 57 to 5,137) days.[118, 121, 122, 131, 136, 166-168, 170, 171] The median age at treatment reported across studies ranged from 10 days (study range: 7 to 24 days) to approximately 393 days (individual study range not reported).[121, 122, 131, 174, 175] Only three studies reported the median time between diagnosis and HSCT, ranging between 28.5 days (study range: 23 to 51 days) and 88 days (study range: 36 to 186 days).[121, 122, 131] These data were often reported according to individual study subgroups (for example, SCID genotype or donor type) as opposed to in aggregate.

All 13 studies reported the donor source (for example, bone marrow) and or donor type (for example, matched family donor) for transplantation.[118, 121, 122, 131, 133, 136, 166-168, 170-173, 175] Ten of the 13 studies reported the conditioning regimens that were used in the study populations.[118, 121, 122, 131, 136, 166-168, 170, 172, 174, 175] These data were typically only reported in aggregate for the total study population.

Table 5.2 Study design and data sources

Study	Region	Centre(s)	Time perspective and study period	Sample size	Median, range (unless specified) follow-up	Data source
Comparative studies focusing specifically on early versus late diagnosis and or HSCT						
Brown 2011[170]	UK	Multiple (n=2)	Retrospective 1979-2010	108	NR	Great Ormond Street Hospital National Health Service Trust/Newcastle General Hospital
Dell Railey 2009[133]	US	Single	Retrospective 1982-2008	161	8.7 (IQR: 2.9-14.1) years, 6 months to 26 years	Duke University Medical Center
Studies describing the impact of a range of factors on survival, including early versus late diagnosis and or HSCT						
Lankester 2021[136]	Europe	Multiple (n=43)	Retrospective 2006-2014	338	4.0 years, 0.2 to 11.8 years	SCETIDE database
Miyamoto 2021[131]	Japan	Multiple (n=NR)	Retrospective 1974-2016	75	3.7 years, 1 day to 28.5 years	Japanese Society of Hematopoietic Cell Transplantation
Haddad 2018[118]	Canada and US	Multiple (n=33)	Retrospective 1982-2012	662	NR	PIDTC
Dvorak 2017[174]	US	Single	Retrospective 1990-2016	83	9.5 years, 1.1 to 26.8 years	Benioff Children's Hospital, University of California
Heimall 2017[122]	Canada and US	Multiple (n=25)	Prospective 2010-2014	100	25 months, 10 to 51 months	PIDTC
Pai 2014[121]	Canada and US	Multiple (n=25)	Retrospective 2000-2009	240	NR	PIDTC
Chan 2011[171]	US	NR	Retrospective NR	158	NR	Immune Deficiency Foundation patient database, the SCID Forum, SCID Angels for Life Foundation
Buckley 2011[167]	US	Single	Retrospective 1982-2010	166	10 years, 2 months to 28.3 years	Duke University Medical Centre
Buckley 2000[166]			Retrospective 1982-2000	112	5.6 years, 3 months to 18.8 years	
Buckley			Retrospective	89	5.6 years, 3 months to 16.5 years	

1999[168]			1982-1999			
Gennery 2010[172]	Europe	Multiple (n=37)	Retrospective 1968-2005	699	1 year, 0.5-2.1 years to 9.6, 0.5-32.6 years*	SCETIDE database
Antoine 2003[175]	Europe	Multiple (n=37)	Retrospective 1968-1999	475	9 years	SCETIDE database
Myers 2002[173]	US	Single	Retrospective 1982-2001	117	Minimum: NR; Maximum: 9 years	Duke University Medical Center

Key: IQR – interquartile range; n – number of centres; NR – not reported; PIDTC – Primary Immune Deficiency Treatment Consortium; SCETIDE – Stem Cell Transplant in Primary Immune Deficiency in Europe

* Data were reported by subtype. Median and range reported for the minimum and maximum presented.

Study descriptions of 'early' versus 'late' diagnosis and or HSCT

The categorisations of 'early' versus 'late' diagnosis and or HSCT, as outlined by the 13 individual studies (with two additional publications linked to one study), [118, 121, 122, 131, 136, 167, 171-173, 175] are described in Table 5.3. As described in section 5.2.1, the cut-offs used within the studies have been re-categorised as 'early' versus 'late' for the present review. The original categorisations used by the studies varied considerably, as follows.

Considering studies which provided data on the impact of early versus late diagnosis, one study specifically compared a group of children diagnosed antenatally or at birth with a group diagnosed after birth; the former ('early') group comprised infants who were diagnosed because of a prior SCID diagnosis in a sibling or family member, and the outcomes of these infants were compared with those of the first presenting family member ('late' group).[170] Three further studies examined groupings based on early versus late diagnosis as part of analyses of a broad range of factors which might affect HSCT outcomes; the first compared infants identified on the basis of family history with those diagnosed clinically,[171] and the remaining two reported numbers of surviving children according to whether they were diagnosed on the basis of family history or NBS, versus those diagnosed clinically.[122, 174]

Among studies which examined the impact of early versus late HSCT, seven studies used a cut-off of receiving HSCT before or after 3.5 months of life.[118, 121, 122, 133, 136, 167, 174] Three of these six studies provided a further broken down comparison based on infection status.[118, 121, 122] Four studies used other ages as HSCT cut-offs for comparison of outcomes; one using 28 days,[173] one using four months,[131] and two using six months.[172, 175]

Table 5.3. Study definitions of "early" and "late" HSCT and or diagnosis*

Study	Sample size			Definition of early	Definition of late
	Early	Late	Total		
Comparative studies focusing specifically on early versus late diagnosis and or HSCT					
Brown 2011[170]	60	48	108	Patients diagnosed during the antenatal period or at birth due to diagnosis of SCID in a previous sibling or family member	First presenting person in the family
Dell Railey 2009[133]	48	113	161	HSCT at ≤3.5 months of age	HSCT at >3.5 months of age
Studies describing the impact of a range of factors on survival, including early versus late diagnosis and or HSCT					
Lankester 2021[136]	91	247	338	HSCT at ≤3.5 months of age	HSCT at >3.5 months of age
Miyamoto 2021[131]	14	61	75**	HSCT at <4 months of age	HSCT at ≥4 months of age
Haddad 2018[118]	130	421	662***	HSCT at <3.5 months of age	HSCT at ≥3.5 months of age (including infection status)
Dvorak 2017[174]	34	49	83	Diagnosis: Family history or NBS Treatment: HSCT at ≤3.5 months of age	Diagnosis: Clinically diagnosed (infection or autoimmunity) Treatment: HSCT at >3.5 months of age
Heimall 2017[122]	56	42	98****	Diagnosis: Diagnosed due to NBS or a positive family history Treatment: HSCT at <3.5 months of age^	Diagnosis: Clinically diagnosed Treatment: HSCT at >3.5 months of age (including infection status)^
Pai 2014[121]	68	172	240	HSCT at ≤3.5 months of age	HSCT at >3.5 months of age (including infection status)
Chan 2011[171]	20	138	158	Diagnosed due to a positive family history (tested at birth)	Clinically diagnosed
Buckley 2011[167]	48	118	166	HSCT at <3.5 months of age	HSCT at ≥3.5 months of age
Buckley 2000[166]	29	83	112		
Buckley 1999[168]	22	67	89		
Gennery 2010[172]	289	398~	699	HSCT at >6 months of age	HSCT at ≥6 months of age
Antoine 2003[175]	202	273	475	HSCT at >6 months of age	HSCT at ≥6 months of age

Myers 2002[173]	21	96	117	HSCT at ≤28 days of age	HSCT at >28 days of age

Key: HSCT - haematopoietic stem cell transplantation; NBS – newborn bloodspot,
* Or diagnostic method as applicable,
** Study sample was 181 overall, but age at HSCT was reported for 75 patients only,
*** n=111 infants missing (that is, not reported),
**** Study sample was 100 overall, but only 98 of 100 patients subsequently received HSCT, ^An age of = 3.5 mo was not defined in the study, ~n=12 patients missing (that is, not reported).

Outcomes of interest

In terms of the primary outcomes of interest, all included studies reported survival-based outcomes. Considering comparisons of groups experiencing early versus late diagnosis and or HSCT, no HSCT-related safety data were provided for the individual groups being compared. A number of studies were noted to describe post-transplant mortality; however, the specific causes were not disaggregated and hence these results are included within the overall survival outcomes described below. The results of this review are outlined below in terms of survival outcomes, secondary outcomes, and the quality appraisal of the included studies.

5.3.3 Survival Outcomes

In terms of the primary outcome of survival, a summary of the overall results of this review is provided below, followed by detailed results presented by study type, with individual study findings also presented in Table 5.4. As previously noted, across the 13 unique studies included, four studies (Brown et al.[170], Heimall et al.[122], Dvorak et al.[174] and Chan et al.[171]), reported on early versus late diagnosis of SCID and provided associated figures for mortality and or survival analysis results, while the remaining studies examined the impact of early versus late HSCT on survival.

Overall summary for survival outcomes

Overall, 12 of the 13 independent studies provided evidence to suggest that early diagnosis and or HSCT led to improved survival outcomes compared with late diagnosis and or HSCT. Three out of four studies which looked at early versus late diagnosis (including identification through testing antenatally and at birth, compared with diagnosis based on clinical presentation) showed improved outcomes in favour of earlier diagnosis, with the third not finding a significant difference in terms of means of diagnosis, but noting a significant effect of age at HSCT. 10 out of 11 studies which included a comparison based on age at HSCT indicated higher survival in those receiving HSCT at an earlier age with the tenth noting a significant impact of the presence of pre-transplant infections (that is, those with previous infections had poorer outcomes compared with those without).

In the context of infection status, eight studies within this review noted that infections prior to HSCT negatively impacted overall survival. Three studies included comparisons of age at HSCT (all using 3.5 months as the cut off) combined with infection status. In those with no history of infection, similar survival rates were noted across the studies in those receiving HSCT before and after 3.5 months of age. In those with active infection at the time of HSCT, survival was higher in those transplanted in the first 3.5 months of life compared with those transplanted at a

later stage. Therefore across the studies included in this review, while outcomes appear more favourable with early diagnosis and or HSCT, infection status at the time of transplant is important, that is, age may serve as a proxy for the condition of the child at the time of HSCT.

5.3.3.1 Comparative studies focusing specifically on early versus late diagnosis and or HSCT

Two comparative studies explicitly set out to compare outcomes in survival associated with early versus late diagnosis with SCID and or receipt of HSCT. A study by **Brown et al.**[170], published in 2011, set out to compare survival for children diagnosed antenatally or at birth versus children diagnosed at a later stage. Brown et al. also investigated whether the survival difference they observed could be accounted for by conditioning regimen, donor type or SCID subtype, and investigated whether the difference could be accounted for by changes in supportive care and transplantation techniques over time. A study by **Dell Railey et al.**[133], published in 2009, aimed to compare long-term outcomes in children with SCID transplanted before 3.5 months of age versus those transplanted after 3.5 months of life. These studies are described as follows.

Brown et al.[170] described a UK cohort of 60 SCID patients diagnosed antenatally or at birth between 1982 and 2010; their diagnosis was made following a diagnosis of SCID in previous family members, and they were therefore referred to as the 'sibling cohort'. These 60 patients were compared with their siblings who had been the first members of the family to present with SCID, having presented for diagnosis between 1979 and 2009 (n = 48); their median age at diagnosis in this cohort was 143.5 days (range 1-455 days) and these patients were referred to as the 'proband cohort'. The authors presented data on rates of mortality within each cohort pre-and post-transplant, as well as overall for the full period of follow-up.

Mortality, both pre- and post-transplant, for each cohort was notably lower in the cohort of children diagnosed at birth. It was noted that fewer (for example, an absence of *pneumocystis jiroveci*) and less severe infections occurred pre-transplant in those diagnosed at birth. This corresponded with the opportunity for early initiation of prophylactic antibiotics and immunoglobulin replacement therapy in this group (in contrast with the 'proband cohort'). All cases of mortality pre-transplant were due to infectious complications; the only case of death in the 'sibling cohort' occurred where the parents refused transplantation for the child.

Considering transplant-related mortality, the substantial survival difference observed between the groups was explored to determine whether it could be explained by

differences in conditioning regimen, donor availability, or SCID subtype. The following findings were observed:

- Within unconditioned transplants, mortality was 50% in the group of children diagnosed later than birth ('proband cohort') versus 10% in the sibling group. The authors concluded on this basis that pre-existing infections were responsible for the high mortality observed in the proband cohort.
- Within donor type, greater mortality was observed in those diagnosed later than birth within the haploidentical transplant subgroup and within the matched family donor transplant group; these differences could not be explained by conditioning regimen used. No differences were observed for other donor subgroups.
- Within genotype, significantly higher mortality was observed in the group diagnosed later than birth for four of eight genotypes examined (including 'undefined'). In the case of ADA-SCID, the mortality difference was attributed to early use of enzyme replacement therapy in the group diagnosed at birth.

Considering mortality throughout follow-up, as of 2010, for those diagnosed antenatally or at birth, 10% overall mortality was observed; this figure included deaths occurring before and after transplantation. This figure was significantly lower ($p<0.001$) than that observed in the series of siblings who were the first in their family to be diagnosed with SCID, of whom 60.4% had died at follow-up. The authors therefore concluded that the improved survival associated with those siblings diagnosed at birth was a result of improved survival both before and after HSCT. Furthermore, the authors suggested that survival after HSCT was improved irrespective of donor choice, conditioning regimen used, or underlying diagnosis (specific form of SCID).

Dell Railey et al.[133] compared long-term outcomes within a US cohort of 161 SCID patients who received HSCT between 1982 and 2008. Patient survival was analysed using Kaplan-Meier survival curves and eight-year survival rates were calculated; these were compared for those transplanted within 3.5 months of life versus after 3.5 months of life, with comparison using the log-rank test. The relationship between age of transplant and survival was also analysed using a Cox proportional hazards regression model. As per Table 5.4, higher eight-year survival was observed in the group who received HSCT in the first 3.5 months of life (96% versus 70%, $p= 0.0017$). Based on Cox proportional hazards regression modelling, patients who were transplanted after 3.5 months were found to have a significantly lower survival rate ($p = 0.0049$), with a hazard ratio of 1.032 per 10-day increase in age at transplant (95% CI 1.01 - 1.06). The authors also observed that clinical

outcomes were superior for patients transplanted within 3.5 months; specifically, those transplanted before the age of 3.5 months were less likely to require a booster transplant, and on long-term follow-up, were less likely to have the outcome of 'clinical problems in the previous two years'.

5.3.3.2 Studies describing the impact of a range of factors on survival, including early versus late diagnosis and or HSCT

In addition to the above studies by Brown et al.[170] and Dell Railey et al.[133], which were focused around analyses comparing survival for 'early' versus 'late' diagnosis and or receipt of HSCT, 11 additional studies of relevance were identified within this review.[118, 121, 122, 131, 136, 166-168, 171-175] These studies reported on, or performed analyses of, survival differences for 'early' versus 'late' groups (amongst a broad range of cohort attributes that may have impacted clinical outcomes); however, this consideration was not the central objective of such studies. These studies are presented in order of publication date, with the most recent studies presented first. Where studies included a multivariable analysis, the included variables are outlined in Appendix 5.2.

Lankester et al.[136], published in 2021, analysed HSCT outcomes in 338 patients who underwent transplantation between 2006 and 2014 and who were registered in the European SCETIDE registry; this study aimed to perform an analysis of immune reconstitution and factors associated with positive clinical outcome. No patients were identified based on newborn screening programmes and the median age at diagnosis was stated as 0.33 years (range 0 – 1 year). The authors considered age at transplantation as a binary variable (set as below or above 3.5 months of life, with patient numbers of n = 91 and n = 247, respectively) and conducted a univariable analysis of the impact of this binary age variable on two-year overall survival and event-free survival (a composite outcome including risk of repeat HSCT, HSCT boost, or death).

Age at transplantation, defined in this way, was not correlated with either two-year overall survival (87.8% versus 82.0%, p = 0.15) or two-year event-free survival (78.8% versus 72.2%, p = 0.45). However, a separate analysis of the impact of pre-transplantation infections found that infections had a strong negative impact on both survival outcomes. On multivariable analysis (see Appendix 5.2), this association held; pre-HSCT infections were associated with significantly poorer overall survival (hazard ratio (HR) = 2.32, 95% confidence interval (CI) 1.44-3.72, p<0.001) and event-free survival (HR = 1.99, 95% CI 1.33 – 2.98, p<0.001) at two years.

Miyamoto et al.[131], published in 2021, described a cohort of 181 SCID patients in Japan who received HSCT between 2006 and 2016; a multivariable analysis (see

Appendix 5.2) was performed to identify factors associated with survival post HSCT, including age at HSCT. Considering patients aged below four months at HSCT (n = 14) versus those who received HSCT at or above the age of four months (n = 61), a significant association with 10-year overall survival was observed on both univariable and multivariable analysis, the latter model having included the following variables: donor type, disease phenotype, bacterial and fungal infection at HSCT, CMV infection prior to HSCT, and conditioning regimen.

Haddad et al.[118], published in 2018, described a cohort of 662 SCID patients treated with HSCT in North America (as part of the Primary Immune Deficiency Treatment Consortium (PIDTC)) from 1982 to 2012; a multivariable analysis (see Appendix 5.2) was performed to determine factors associated with survival and immune reconstitution in non- matched sibling donor (MSD) HSCT recipients, and included age and infection status at HSCT, amongst other factors such as genotype, conditioning regimen and clinical presentation.

On multivariable analysis, younger age at HSCT (<3.5 months of age) and absence of infection at HSCT were associated with improved 10-year survival, with interaction occurring between these factors. In particular, among patients with active infection at the time of HSCT (discussed further below), survival was significantly improved in patients who underwent HSCT within 3.5 months of life versus at a later age (HR = 0.29, 95% CI 0.11 – 0.74).

Dvorak et al.[174], published in 2017, described a cohort of 83 children with SCID who underwent HSCT at a single centre in California between 1990 and 2016. Using univariable analyses, the authors separately considered the impact of the means of identification (that is, family history, NBS, or clinical) and age at HSCT (that is, before or after 3.5 months of life) on five-year overall survival. Higher survival rates were observed for children identified through family history or NBS compared with those identified based on clinical presentation (100% [95% CI 73 to 100] versus 90% [95% CI 77 to 100] versus [67%, 95% CI 54 to 80], respectively; p = 0.02). Similarly, treatment with HSCT before 3.5 months was associated with higher survival than treatment after 3.5 months (92% [95% CI 84 to 100] versus 66% [95% CI 52 to 70], p = 0.002). The authors further investigated the impact of these factors on neurological outcomes; these results are described further under 'secondary outcomes' in section 5.3.4, below.

Heimall et al.[122], published in 2017, described a cohort of patients treated with HSCT in North America (as part of the PIDTC) from 2010 to 2014, and investigated factors which might impact survival, including method of diagnosis (NBS or family history versus clinical presentation), infection at the time of transplant, and age at time of transplant (within 3.5 months of life versus above 3.5 months). Probabilities

of two-year overall survival were calculated using the Kaplan-Meier method, with univariable comparisons conducted using the log-rank test. Patients who were diagnosed by newborn bloodspot screening had a similar two-year overall survival to those diagnosed by other means (90% versus 90%; p = 0.67). Patients transplanted at 3.5 months of age (regardless of infection status) were found to have a two-year overall survival of 92% (95% CI 78-97), which compared with 96% (95% CI 76-99) for patients transplanted at above 3.5 months of age and who were free of infection at HSCT, and 80% (95% CI 61-90) for transplant patients who were above 3.5 months of age with an active infection (p = 0.036). The impact of infection status on survival is discussed further below.

This 80% two-year survival rate in those with an active infection and who were transplanted at or above 3.5 months of age was noted by the authors to be higher than that reported for patients from the same consortium who were transplanted between 2000 to 2009,[(121)] (see Pai et al. below). The authors suggested that improvements in supportive care before and during HSCT may partly explain the similar survival rates for those whose disease was detected clinically compared with those detected via NBS, as well as the greatly improved survival rate of patients transplanted at or above 3.5 months of age who had an active infection at the time of transplant.

Pai et al.[(121)], published in 2014, described a cohort of 240 infants with SCID who received HSCT at 25 centres in North America (as part of the PIDTC) between 2000 and 2009. A multivariable analysis (see Appendix 5.2) was performed to identify factors associated with survival post HSCT at five years, one of which was a multi-level variable incorporating age at transplantation and infection status. Infants who received HSCT after 3.5 months of life were compared in terms of three subgroups (no infection, active infection at the time of transplant, infection resolved) with infants who received HSCT within 3.5 months of life. Those who received HSCT 'late' and who had active infection at the time of transplant were 11 times more likely to have died (p < 0.001) at five years follow-up than those in the 'early' group. However, no association was observed for those in the 'late' group who had no infection (HR = 1.03, p = 0.97), and there was a weak, non-significant association for those with a resolved infection (HR = 2.88, p = 0.07). The impact of infection status is discussed further below.

Chan et al.[(171)], published in 2011, performed a survey of parents of children with SCID. The authors highlight that a higher proportion of those tested at birth due to a family history of SCID (n = 20) were alive at the time of survey compared to those diagnosed clinically (n = 138) (85% versus 58%, p = 0.026).

Buckley et al.[166-168], were three linked updates of a study, published in 1999, 2000, and 2011, which described a cohort of patients treated with HSCT in the US who received HSCT in the 28.3 years leading up to the final publication study (between 1982 and 2011). The studies investigated the long-term outcomes of consecutive patients with SCID who received non-conditioned, related donor HSCT at the institution. The proportions of patients who were still alive at the time of the reporting (in all three publications) were higher in patients receiving HSCT within 3.5 months of life compared with patients receiving HSCT after 3.5 months of age (94% versus 69%, p = <0.001 in the most recent study). As part of the discussion of this paper, the authors suggested that there is a high probability of success for patients receiving HSCT from a relative performed in the first 3.5 months of age, before infections develop.

Gennery et al.[172], published in 2010, described long-term HSCT outcomes in 699 patients who underwent transplantation between 1968 and 2005 and who were registered in the European SCETIDE registry. The log-rank test was used to compare survival between different groups, and a Cox proportional hazard model with a stepwise forward selection process was used to evaluate the impact of independent factors, including demographics, comorbidity, transplant characteristics, and therapeutics before HSCT, on patient survival (see Appendix 5.2). The probability of survival at 10 years was longer for patients receiving HSCT at less than six months of age (68%, 95% CI 62-74), versus patients receiving HSCT at six to 11 months of age (59%, 95% CI 53-67), or patients receiving HSCT at older than 12 months of age (51%, 95% CI 42-61) (p=0.0008).

On multivariable analysis (see Appendix 5.2), this association held; HSCT at less than six months of age was associated with better overall survival. This difference was statistically significant when compared with patients receiving HSCT at 12 months or older (HR: 2.4, 95% CI 1.6-3.5 p<0.001), but was not when compared to patients who received HSCT between 6 and 11 months of age (HR = 1.3, 95% CI 0.9-1.9, p=0.11). The authors suggested that, for patients with no pre-existing infection, such as newborns, survival is improved with transplant occurring before six months of age.

Antoine et al.[175], published in 2003, described HSCT outcomes in 475 patients who underwent transplantation between 1968 and 1999 and who were registered in the European SCETIDE registry; this study aimed to analyse the long-term results of HSCT in primary immunodeficiencies. While this study included SCID patients from the same database as **Gennery et al.[172]**, the variable for age at HSCT was only provided for patients who received HLA-identical transplantation in this publication. Survival probabilities were calculated using a Cox proportional hazards model, which

assessed the impact of independent predictors (including demographics, comorbidity, transplant characteristics, and therapy before transplantation).

The probability of survival at three years post HSCT was longer for patients receiving HSCT at less than six months of age (85%, 95% CI 77-93), versus patients receiving HSCT at six to 11 months of age (73%, 95% CI 59-86), or patients receiving HSCT at older than 12 months of age (53%, 95% CI 35-71, p=0.0004). On multivariable analysis (see Appendix 5.2), this association held; HSCT at less than six months of age was associated with better overall survival. This difference was statistically significant when compared with patients receiving HSCT at 12 months or older (HR: 8.3, 95% CI 2.7-25.4, p<0.001), but was not when compared to patients who received HSCT between 6 and 11 months of age (HR = 2.2, 95% CI 0.9-5.6, p=0.12). The authors additionally noted that the outcomes for patients receiving HSCT have improved over time. They speculated that this was most likely indicative of improvements in prevention or in treatment of complications, including infections and graft versus host disease, as opposed to earlier diagnosis; this was suggested to be the case as the authors noted that the frequency of pre-transplantation complications and age at transplantation had not changed over time.

Myers et al.[173], published in 2002, performed a retrospective study which aimed to compare the development of immune function post HSCT in 21 infants who received HSCT in the first 28 days of life; as part of the discussion of this paper, the authors compared survival in this group with that of 96 patients who received HSCT after 28 days of life. It was noted that all but one of the 21 infants in the 'early' group (95%) had survived post HSCT at the time of the publication, with the period of survival ranging from 8 months to more than 19.2 years post HSCT; this compared with a 74% survival rate in the 96 infants who received HSCT after the first 28 days of life.

Presence of pre-HSCT infections

Eight studies reported the effect of pre-HSCT infections on survival outcomes.[118, 121, 122, 131, 136, 172, 175] Of note, one of these studies only provided data for patients receiving transplantations from related HLA-mismatched donors.[175] All seven studies found that infections prior to HSCT negatively impacted overall survival.[118, 121, 122, 131, 136, 172, 175]

In three of the studies, all representing independent cohorts from the PIDTC in North America, infection status prior to HSCT and the age at HSCT were intrinsically linked.[118, 121, 122] One of these reported on infants who received transplants between 2000 and 2009, and noted that, among children aged older than 3.5 months at the time of HSCT, those with no history of infection had a five-year

survival rate of 90%, while those with a resolved infection had a survival rate of 82%. This was contrasted with infants aged older than 3.5 months at transplant and who had active infection, in whom survival was 50%. In the multivariable model of various factors affecting survival, the combined variable incorporating age at transplantation (above or below 3.5 months) and infection status (none, active infection, or resolved infection) was statistically significant ($p<0.001$).[121]

Furthermore, the likelihood of having an active infection at the time of HSCT was significantly higher in patients that received HSCT when older than 3.5 months of age (53%), compared with those that were younger (22%, $p<0.001$).[121]

Another study also reported that active infection was less common in those transplanted at less than 3.5 months compared with those who were older (66% infection-free versus 46% infection-free, $p<0.001$).[122] The study also reported that two-year overall survival was higher in those transplanted at less than 3.5 months of age regardless of infection status (92%) and in those transplanted at 3.5 months or older who were also infection-free at HSCT (96%) than in those transplanted at 3.5 months or older who had an active infection at HSCT (80%, $p=0.036$).[122]

The final study demonstrated that infection status significantly impacted 10-year overall survival in those who underwent HSCT at older than 3.5 months of age, but not those that were younger than 3.5 months.[118] The study found that, among those with active infection at HSCT, overall survival was higher in those that received HSCT at younger than 3.5 months than those who underwent HSCT at an older age (HR: 0.29, 95% CI: 0.11 to 0.74, $p=0.009$).[118]

One study (based on data collected between 2006 and 2014 from multiple European centres) found that pre-transplant infection had a negative impact on survival, with a two-year overall survival of 73.0% in those with pre-transplant infections compared with 86.6% in those without. Event free survival also differed with two-year rates of 65.5% and 79.9%, respectively.[136] Another European based study further noted that the absence of viral infections prior to HSCT was associated with higher 10 year-survival (63% versus 52%) which retained significance in a multivariate analysis.[172]

A study from Japan noted that within univariate analyses 10-year overall survival was higher in those without bacterial or fungal infection at HSCT (75% versus 50%) and for those without prior cytomegalovirus (CMV) infection (71% versus 33%), with these findings maintained within a multivariate analysis including age, phenotype, donor type, and conditioning regimen.[131] A US-based study including 83 children treated with HSCT at a single centre between 1990 and 2016 noted that pre-HSCT

infections were associated with lower fiver-year overall survival (63% versus 97%, p<0.004).[174]

Table 5.4 Survival-based outcomes reported across studies

Study first author, year of publication	Setting	Definition of 'early' versus 'late' comparison groups	Outcome investigated / reported	Outcome in 'early' group (N or % survived)	Outcome in 'late' group (N or % survived)	Statistical test of difference reported by authors
Comparative studies focusing specifically on early versus late diagnosis and or HSCT						
Brown 2011[170]	UK, patients diagnosed with SCID from 1979 – 2010.	Early: Diagnosed antenatally/at birth (siblings of children in the 'late' group) (N = 60) Late: First members of a family to be diagnosed. Median age at diagnosis = 143.5 days. (N = 48)	Survival pre HSCT:	59/60 (98.2%) survived	31/48 (64.6%) survived	-
			HSCT-related survival (or survival post gene therapy):	54/59 (91.5%) survived	19/31 (61.3%) survived	p < 0.001
			Overall survival (based on data available at study publication):	54/60 (90.0%) survived	19/48 (39.6%) survived	p < 0.001
			Subgroup analysis: Survival of sibling sets transplanted within 10 years of each other:	29/31 (93.5%) survived	13/24 (54.2%) survived	p < 0.01
Dell Railey 2009[133]	US, patients diagnosed with SCID who received HSCT from 1982 – 2008.	Early: HSCT within 3.5 months of life (N = 48) Late: HSCT after 3.5 months of life	8-year survival (Kaplan-Meier analysis)	96% survival (95% CI 84 - 99) *Median duration of follow-up: 9.2 years*	70% survival (95% CI 60 -77) *Median duration of follow-up: 8.5 years*	p = 0.0017

Study first author, year of publication	Setting	Definition of 'early' versus 'late' comparison groups	Outcome investigated / reported	Outcome in 'early' group (N or % survived)	Outcome in 'late' group (N or % survived)	Statistical test of difference reported by authors
		(N = 113)				
Studies describing the impact of a range of factors on survival, including early versus late diagnosis and or HSCT						
Lankester 2021[136]	SCETIDE SCID registry, patients who received HSCT from 2006 – 2014	Early: HSCT within 3.5 months of life (N = 91) Late: HSCT after 3.5 months of life (N = 247)	2-year overall survival	87.8% survived	82.0% survived	p = 0.15
			2-year event-free survival (second HSCT, HSCT boost, death)	78.8% survived	72.2% survived	p = 0.45
Miyamoto 2021[131]	Japan, patients diagnosed with SCID who received HSCT from 2006 - 2016	Early: HSCT within 4 months of life (N = 14) Late: HSCT after 4 months of life (N = 61)	10-year overall survival (Kaplan-Meier analysis)	84% survival (95% CI 63- 84)	56% survival (95% CI 48 – 64%)	p = 0.02
Haddad 2018[118]	US, patients treated with HSCT from 1982 to 2012 as part of the Primary Immune Deficiency Treatment	Early: HSCT within 3.5 months of life (N = 130):	10-year mortality and overall survival in non-MSD HSCT, estimated using multivariable analysis.	No infection: 75/87 (86.2%) survived	No infection: 33/43 (76.7%) survived	p = 0.470 Late vs early, no infection: HR = 1.37 (95% CI 0.58 – 3.24)

Study first author, year of publication	Setting	Definition of 'early' versus 'late' comparison groups	Outcome investigated / reported	Outcome in 'early' group (N or % survived)	Outcome in 'late' group (N or % survived)	Statistical test of difference reported by authors
	Consortium.	Late: HSCT after 3.5 months of life (N = 421)	Multivariable analysis results are presented in the 'statistical test of difference' column, in terms of pairwise comparison p-values and HR.	Active infection: 21/26 (80.8%) survived	Active infection: 130/240 (54.2%) survived	p = 0.009 Early vs late, active infection: HR = 0.29 (95% CI 0.11 – 0.74)
				Resolved infection: 16/17 (94.1%) survived	Resolved infection: 96/138 (69.6%) survived	(Result not reported)
Dvorak 2017[174]	US, patients treated with HSCT from 1990 to 2016 at the University of California	Early (1): Diagnosis via NBS or family history Late (1): Diagnosis occurring clinically	Univariable analyses for five-year overall survival, five-year cumulative incidence of neurologic events, and five-year neurologic event-free survival. Multivariable analysis for five-	Five year overall survival: ▪ Family history: 100% (95% CI 73 to 100) ▪ NBS: 90% (95% CI 77 to 100)	Five year overall survival: 67% (95% CI 54 to 80)	p = 0.02
		Early (2): HSCT within 3.5 months of life		Five year overall survival: 92% (95% CI 84-100)	Five year overall survival: 66% (95% CI 52-70)	p = 0.002

Study first author, year of publication	Setting	Definition of 'early' versus 'late' comparison groups	Outcome investigated / reported	Outcome in 'early' group (N or % survived)	Outcome in 'late' group (N or % survived)	Statistical test of difference reported by authors
		Late (2): HSCT beyond 3.5 months of life.	year neurologic event-free survival. **Note:** SCID genotypes of ADA, AK2, and BCL11B excluded from analyses due to potential for neurological impairment from underlying deficiencies.			
Heimall 2017[122]	North America, patients diagnosed with SCID who received HSCT from 2010 – 2014.	Early (1): Diagnosis via NBS or family history Late (1): Diagnosis occurring clinically	2-year overall survival	90% survived	90% survived	p = 0.67
		Early (2): HSCT within 3.5 months of life Late (2): HSCT beyond 3.5 months of life. 'Late (2)' included 'infection-free' and	2-year overall survival	92% (95% CI 78 – 97) survived	Infection-free: 96% (95% CI 76 – 99) survived Active infection: 80% (95% CI 61 – 90) survived	p = 0.036

Study first author, year of publication	Setting	Definition of 'early' versus 'late' comparison groups	Outcome investigated / reported	Outcome in 'early' group (N or % survived)	Outcome in 'late' group (N or % survived)	Statistical test of difference reported by authors
		'active infection' subgroups.				
Pai 2014[121]	North America, patients diagnosed with SCID who received HSCT from 2000 – 2009.	Early: HSCT within first 3.5 months of life Late: HSCT after 3.5 months of life. Subgroups within 'late' included 'no infection', 'active infection', and 'resolved infection'.	5-year overall survival	94% (95% CI 85 – 98) survived	No infection: 90% (95% CI 67 – 98) survived Active infection: 50% (95% CI 39 – 61) survived Infection resolved: 82% (95% CI 70 - 90)	p < 0.001 *(test of significance of overall variable in separate multivariable model)*
Chan 2011[171]	US, survey sent to parents from the Immune Deficiency Foundation patient database, subscribers of the SCID Forum database, and members of the SCID Angels for Life Foundation.	Early: Diagnosed due to a positive family history (tested at birth) (N = 20) Late: Clinically diagnosed (not tested at birth)(N = 138)	Proportion of patients surviving at the time of reporting (2011), follow up time not reported.	85% survival	58% survival	p = 0.026
Buckley 2011[167]	US, patients diagnosed with SCID who received	Early: HSCT within 3.5 months of life (N = 48)	Proportion of patients surviving at the time of	44/48; 94% survival	82/118; 69% survival	p < 0.001

Study first author, year of publication	Setting	Definition of 'early' versus 'late' comparison groups	Outcome investigated / reported	Outcome in 'early' group (N or % survived)	Outcome in 'late' group (N or % survived)	Statistical test of difference reported by authors
	HSCT in the 28.3 years leading up to the study.	Late: HSCT after 3.5 months of life (N = 83)	reporting (2011), based on a range of 2 months to 28.3 years follow up.			
Buckley 2000[166] Note: Linked study, see Buckley et al. (2011) for main results	US, patients diagnosed with SCID who received HSCT in the 18.8 years leading up to the study.	Early: HSCT within 3.5 months of life (N = 29) Late: HSCT after 3.5 months of life (N = 83)	Proportion of patients surviving at the time of reporting (2000), based on a range of 3 months to 18.8 years follow-up.	28/29; 96.6% survival	61/83; 73% survival	NR
Buckley 1999[168] Note: Linked study, see Buckley et al. (2011) for main results	US, patients diagnosed with SCID who received HSCT in the 16.5 years leading up to the study.	Early: HSCT within 3.5 months of life (N = 22) Late: HSCT after 3.5 months of life (N = 67)	Proportion of patients surviving at the time of reporting (1999), based on a range of 3 months to 16.5 years follow-up.	21/22; 95% survival	51/67; 76% survival	p = 0.088
Gennery 2010[172]	SCETIDE SCID registry, patients who received HSCT from 1968 – 2005.	Early: HSCT within 6 months of life (N = 289) Late: HSCT after 6 months of life (N = 398)	10-year overall survival	68% (95% CI 62-74) survived	HSCT from 6-11 months of life: 59% (95% CI 53-67) survived HSCT after 12 months of life:	p = 0.008 *(test of significance of overall variable in the three*

Study first author, year of publication	Setting	Definition of 'early' versus 'late' comparison groups	Outcome investigated / reported	Outcome in 'early' group (N or % survived)	Outcome in 'late' group (N or % survived)	Statistical test of difference reported by authors
		Subgroups within 'late' include HSCT from 6-11 months of life (N = 253) and HSCT after 12 months of life (N = 145).			51% (95% CI 42-61) survived	*different groups)*
Antoine 2003[175]	SCETIDE SCID registry, patients who received HSCT from 1968-1999. Only results for patients who received HLA-identical transplantation are presented for 'early' versus 'late' comparisons.	Early: HSCT within 6 months of life (N = 92) Late: HSCT after 6 months of life (N = 81) Subgroups within 'late' include HSCT from 6-11 months of life (N = 50) and HSCT after 12 months of life (N = 31).	3-year overall survival	85 % (95% CI 77-93) survival	HSCT from 6-11 months of life: 73% (95% CI 59-86) survival HSCT after 12 months of life: 53% (95% CI 35-71) survival	P = 0.0004 *(univariable test of significance of overall variable considering three different groups)*
Myers 2002[173]	US, patients diagnosed with SCID who received HSCT in the 19.2 years leading up to the study.	Early: HSCT within 28 days of life (N= 21) Late: HSCT after 28 days of life	Proportion of patients surviving at the time of reporting (2002), based on a range of 8 months to	95% survived	74% survival	-

Study first author, year of publication	Setting	Definition of 'early' versus 'late' comparison groups	Outcome investigated / reported	Outcome in 'early' group (N or % survived)	Outcome in 'late' group (N or % survived)	Statistical test of difference reported by authors
		(N=96)	>19.2 years follow-up			

Key: HLA - human leukocyte antigen, HSCT, haematopoietic stem cell transplantation, HR – hazard ratio, IQR – interquartile range, n – number of centres, NR – not reported, PIDTC – Primary Immune Deficiency Treatment Consortium, SCETIDE – Stem Cell Transplant in Primary Immune Deficiency in Europe, SCID – severe combined immunodeficiency,

Note: All results for outcomes detailed above represent univariable analyses of differences, unless otherwise specified. Results of multivariable analyses, where performed, are described in the accompanying text description for the studies.

Analyses comparing across time periods

Given the rarity of SCID, many of the studies included clinical data from across several decades in their analysis (see Table 5.5). During this time, there have been improvements in supportive care and transplantation-related techniques (such as in the available conditioning regimens and GvHD prophylaxis). Accordingly, eight studies conducted sub-cohort analyses to investigate whether the time period in which transplantation was conducted translated into better outcomes for patients with SCID.[118, 131, 136, 170-172, 174, 175]

Five of the eight studies found that survival outcomes improved for all infants over time.[131, 170, 172, 174, 175] One of these studies also found that, based on analysis of infants that were transplanted within 10 years of each other, survival was consistently better for infants that were diagnosed at birth compared with the first presenting person in the family (93% versus 54%, $p<0.01$).[170]

Three studies found that there was no significant difference in survival outcomes between the time periods investigated.[118, 136, 171] The first of these studies compared data from 2006 to 2010 with data from 2011 to 2014.[136] The second of these studies found that overall survival was similar across decades analysed (1980-1989, 1990-1999 and 2000-2012), with treatment failure for patients who initially received non-MSD HSCT becoming more frequent in the most recent decade (of note, analyses for this outcome in MSD recipients were not reported).[118] The third study found that infants born in 2000 or later had slightly higher survival, but this was result was not statistically significant.[171]

Table 5.5 Sub-cohort analyses of study time periods

Study	Study period	Sub-cohort analyses	Key findings
Lankester 2021[136]	2006-2014	Year of transplantation ▪ 2006-2010 ▪ 2011-2014	▪ no significant difference in OS and EFS
Miyamoto 2021[131]	1974-2016	Year of transplantation ▪ 1974-2005 ▪ 2006-2016	▪ no significant difference in OS (p=0.14)
Haddad 2018[118]	1982-2012	Decade ▪ 1980-1989 ▪ 1990-1999 ▪ 2000-2012	▪ OS was similar across decades (p = 0.970) ▪ described as an 'unexpected finding', treatment failure for patients who initially received non-MSD transplantation became more frequent in recent decade (p = 0.006)
Dvorak 2017[174]	1990-2016	Year of transplantation ▪ 1990-2004 ▪ 2005-2016	▪ five-year OS (p = 0.02) higher in those transplanted after 2005 ▪ five-year neurological event-free survival higher for those transplanted after 2005 (p = 0.04) ▪ no significant difference for five-year cumulative incidence of neurologic events (p = 0.81)
Brown 2011[170]	1979-2010	analysis of diagnosis at birth/ siblings not diagnosed at birth that were transplanted within 10 years of each other	▪ survival was consistently better for infants that were diagnosed at birth (94% versus 54%, p < 0.01).
Chan 2011[171]	NR	Year of birth ▪ pre-1995 ▪ 1995-1999 ▪ 2000 or later	▪ infants born in 2000 or later had slightly higher survival, but non-significant
Gennery 2010[172]	1968-2005	Year of transplantation ▪ pre-1995 ▪ 1995-1999 ▪ 2000-2005	▪ 10-year OS improved over time (p < 0.001), however there is no difference in the two most recent periods.
Antoine 2003[175]	1968-1999	Year of transplantation ▪ 1968-1985 ▪ 1986-1990 ▪ 1991-1995 ▪ 1996-1999	▪ frequency of acute GvHD decreased over time after haploidentical transplantation, from 35–40% before 1996 to 22% thereafter (p < 0.001) ▪ better survival with time (data not clearly reported).

Key: EFS – event-free survival, GvHD – graft-versus-host disease, MSD – matched sibling donor, NR – not reported, OS – overall survival

5.3.4 Secondary outcomes

Neurological outcomes

One study from the US,[174] assessed neurological-based outcomes. This study comprised a cohort of 83 children with SCID who underwent HSCT at a single centre in California between 1990 and 2016. The study presents univariable analyses to assess the impact of the means of identification (that is, family history, NBS, or clinical) and age at HSCT (that is, before or after 3.5 months of life) on the five-year cumulative incidence of neurologic events and five-year neurologic event-free survival. Severe neurological impairments were considered and defined as the presence of one or more of: cerebral palsy/hemiplegia, blindness, severe developmental delay or a chronic seizure disorder. Of note, the authors excluded the SCID genotypes of ADA-SCID, AK2, and BCL11B from analyses due to potential for neurological impairment from underlying deficiencies.

A lower five-year cumulative incidence of neurologic events was observed in children identified through family history or NBS than in those identified based on clinical presentation (0% [95% CI 0 to 27] versus 0% [95% CI 0 to 18] versus 20% [95% CI 7 to 23], respectively; p = 0.03). Similarly, five-year neurologic event-free survival was statistically higher in those identified on the basis of family history (100%, 95% CI 72 to 100) or NBS (90%, 95% CI 77 to 100) compared to those identified clinically (51%, 95% CI 37 to 65). Those treated with HSCT before 3.5 months of life had a lower five-year cumulative incidence of neurologic events (3% [95% CI 1 to 7] versus 20% [95% CI 7 to 34], p = 0.02) and higher five-year neurologic event-free survival (90% [95% CI 80 to 99] versus 50% [95% CI 35 to 65], p <0.001) than those treated after 3.5 months.

The presence of pre-HSCT infections was associated with a statistically significant lower five-year cumulative incidence and a higher five-year neurologic event-free survival. On multivariable analysis (the only one completed), only the presence of pre-HSCT infections was significantly associated with a lower five-year neurologic event-free survival (HR 8.23, 95% CI 2.8 to 27.3, p<0.001). However, there was a high correlation observed between the means of diagnosis (diagnosis via either NBS or family history, versus clinical) and infection status (κ = 0.9, 95% CI 0.85-0.95, p<0.001).

Need for repeat HSCT or stem cell boosts

The impact of HSCT timing on the need for repeat transplantation was reported in three studies.[118, 133, 166-168] Both studies from Duke University Medical Center in the US (that is, Dell Railey et al.[133] and Buckley et al.[167]) reported that the need for a second transplant was more common in those that underwent HSCT at an age older

than 3.5 months.[133, 166-168] The other study (from Canada and the US) conducted by Haddad et al.[118] found, based on a multivariable analysis specifically considering recipients of non-MSD donor cells, age and infection status at HSCT (namely those undergoing HSCT over the age of 3.5 months with active or resolved infections) were associated with treatment failure and need for second treatment (described as either HSCT, enzyme replacement therapy, or gene therapy); analyses for MSD were not presented.[118]

Immune reconstitution

Appropriate immune reconstitution is a significant contributor to long-term quality of life in patients with SCID after undergoing HSCT, and can be evaluated in several ways, including examination of:

- T-cell subpopulations (indicative of thymic output)
- the degree of B-cell reconstitution (the use of Ig replacement therapy can indicate a lack of B-cell engraftment)
- donor lymphocyte chimerism (that is, how well donor lymphoid cells have durably engrafted in the recipient).[176, 177]

Nine of the 12 included independent studies presented outcomes with respect to immune reconstitution in patients post-HSCT, [118, 121, 122, 131, 133, 136, 166-168, 170, 173] with five reporting on the impact of HSCT timing,[118, 136, 166-168, 170, 173] including two studies based on retrospective data collected between 1982 and 2010 in Duke University Medical Center in the US.[166-168, 173] Both studies found that transplantation at an earlier age led to improvements in immune reconstitution. The study by Buckley et al.[167] (from Duke University Medical Center, US) reported improved immune reconstitution for infants that were transplanted in the neonatal period compared with those that were transplanted later.[166-168] Specifically, the authors noted the following improvements for infants transplanted in the neonatal period:

- higher lymphocyte responses to phytohaemagglutinin and higher numbers of CD3+ and CD45RA+ T cells in the first three years of life ($p<0.05$)
- peaking of TREC levels occurred earlier (between 181 days and one year compared with between one and three years in those transplanted later) and at higher TREC values ($p<0.01$).[166-168]

One study found that age at HSCT impacted the development of lymphocyte subsets, lymphocyte proliferation and thymus function.[173] Infants that received

HSCT by 28 days of age demonstrated increased lymphocyte proliferation to phytohaemagglutinin, and higher numbers of $CD3^+$ and $CD45RA^+$ T cells, when compared with those that were transplanted at an older age, with the difference in T-cell reconstitution most evident between three months and three years following HSCT. These differences can be attributed to higher thymic output post-HSCT and the potential for an infant to have experienced recurrent or opportunistic infections, malnutrition and or failure-to-thrive prior to receiving HSCT. However, B-cell function did not improve following early HSCT.[173]

In contrast to the studies from Duke University Medical Center, the other three studies found that age at HSCT did not impact immune reconstitution.[118, 136, 170] Two of these studies compared patients younger and older than 3.5 months at the time of HSCT (with one including infection status combined with age).[118, 136] The third study, comparing outcomes of infants in the UK that were diagnosed because of a prior SCID diagnosis in a sibling or family member with those of the first presenting family members, reported no difference in terms of T-cell recovery one-year post-HSCT or humoral immune reconstitution.[170]

Pai et al. reported that active infection at HSCT was associated with inferior CD3+ T-cell recovery when compared with those that had no history of infection and those whose infection had resolved by HSCT ($p=0.009$).[121]

Other outcomes

Two studies reported on differences in growth percentiles between patients with SCID who received HSCT within the first 3.5 months of life or after; outcomes for height and weight were expressed in terms of whether the children were above or below the third percentile of the population.[133, 167] One study found that the proportion of patients below the third percentile for height was smaller for patients who received early compared with late HSCT (5% and 17%, respectively), although this difference was not statistically significant.[133] The second study found a statistically significant difference in terms of the percentage of patients below the third percentile for weight; this finding was also in favour of those who received early HSCT compared with those who received late HSCT.[167]

5.3.5 Quality appraisal

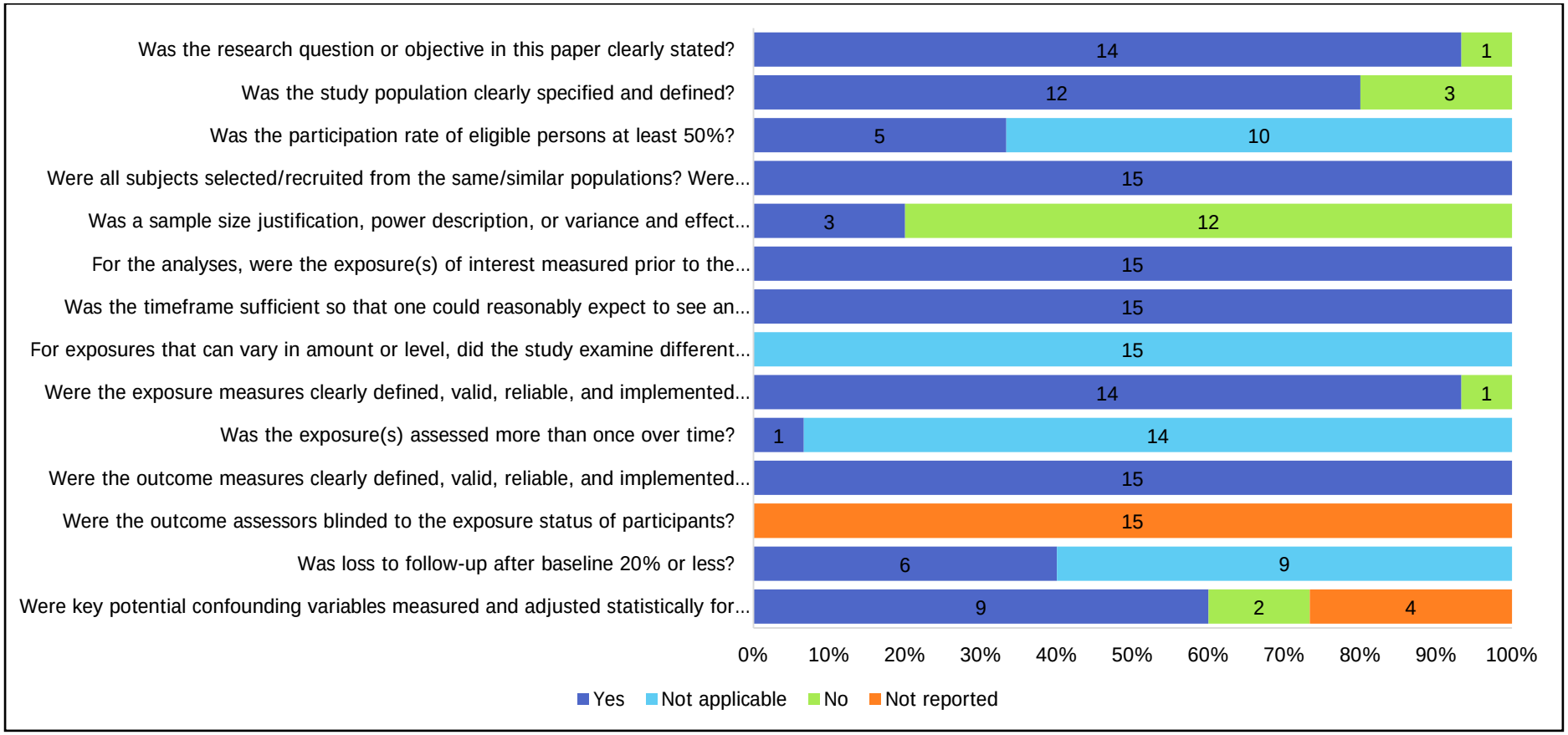
This systematic review identified two comparative studies in which study participants were stratified into two independent groups with the studies specifically comparing groups based on whether or not the infant received an early SCID diagnosis and or access to HSCT; that is, the exposure of central interest to the review question being considered.[133, 170] The other 11 independent studies considered the potential effect of early diagnosis and or treatment amongst a broad range of factors that could

have impacted clinical outcomes; thus, many exposures were considered as part of a greater descriptive analysis of factors associated with HSCT outcomes.[118, 121, 122, 131, 136, 166-168, 171, 172, 174, 175] Such studies may identify associations worthy of further exploration to identify whether they are causal factors, but are not designed to assess causal inference, and therefore differ from conventional cohort studies designed to assess a particular exposure.

No clear tool for appraising the quality of descriptive studies was identified; however the NIH quality assessment tool for observational cohort and cross-sectional studies was used as a guide to assist in identifying individual study quality (Figure 5.2). Accordingly, a summary quality rating was not assigned and the tool was instead used to facilitate the discussion and identification of key quality and reporting issues. There were two quality and reporting issues that were common across a number of studies. Firstly, three independent studies did not clearly specify and define the study population (for example, not reporting relevant demographic details and or participant characteristics).[166-168, 170, 172] Secondly, discussion of potential limitations arising from a lack of statistical power was provided in only two of the 13 studies.[171, 172] This was not described by the other 11 studies.[118, 121, 122, 131, 133, 136, 166-168, 170, 173, 174] Eight studies provided sufficient information to suggest that there was adequate adjustment for potential confounding in their statistical analysis;[118, 121, 122, 131, 136, 170, 172, 174] these confounders generally related to infection status, the use of conditioning and donor type or source. While the remaining studies did not provide information on adjusting for potential confounding, this was not considered to be a reporting or quality issue.[133, 166-168, 171, 173] The model selections may have been appropriate for the objectives of the study authors, but as the majority of the studies were not designed to assess the independent impact of a single exposure of interest; the multivariable models used do not represent appropriate adjustment for confounding of the association of central interest to this review.

A key generalisability issue identified across several studies was that much of the included study data were collected across multiple decades and extended as far back as the year 1968. This is a direct consequence of the rare and heterogeneous nature of SCID which requires researchers to collate data over extended periods of time to ensure sufficient sample coverage for conducting study analysis. However, such data are of limited applicability to current clinical practice due to the substantial improvements in HSCT-related techniques and supportive care that have occurred over time.

Figure 5.2 Summary risk of bias plot



5.4 Discussion

The purpose of this chapter was to identify and assess the currently available international evidence of the clinical effectiveness and safety of early diagnosis and or HSCT, compared with late diagnosis and or HSCT, in children with SCID. Fifteen publications, comprising 13 independent studies, were included in the systematic review. Each of the studies followed a cohort study design. Two studies were based around the exposure of central interest to this review, stratifying participants into two independent groups and specifically comparing these groups based on whether or not the infant received an early SCID diagnosis and or access to HSCT, while the remaining studies considered the potential effect of early diagnosis and or HSCT amongst a broad range of factors that could have impacted clinical outcomes. All of the included studies reported survival-based outcomes; however, no specific safety data (for example, transplant-specific complications) were reported for the comparison of 'early' versus 'late' HSCT. While a number of studies provided figures for post-transplant mortality, the specific causes were not disaggregated and the results were therefore described in this report in the context of overall survival outcomes.

The description of early versus late was heterogeneous across the studies, including definition based on the means of diagnosis (that is NBS, family history, or symptomatic presentation) and age at HSCT. The majority of studies categorised by age at HSCT; however, variability was noted in the cut-offs used, with 3.5 months being most frequently reported, but cut-offs of 28 days, four months, and six months also used. A number of studies further considered infection status alongside age at HSCT. It should be noted that while only four studies identified within this review considered early versus late diagnosis (the key question in the context of a screening programme), the remaining studies which provided evidence based on age at HSCT are still considered relevant to the research question. This relevance is evident from the historical Irish data outlined in chapter three, indicating that the median age at definitive treatment was 184 days, or approximately six months, for those diagnosed clinically based on symptomatic presentation (compared with 54 days for those identified by risk-based detection at birth). Overall, twelve of the 13 independent studies provided evidence to suggest that early diagnosis and or HSCT led to improved survival outcomes, compared with late diagnosis and or HSCT. Of note, while outcomes appeared more favourable with early diagnosis and or HSCT, infection status at the time of transplant appeared to be particularly important. One study included neurological outcomes, with early HSCT (before 3.5 months age) and identification on the basis of family history or NBS associated with better outcomes overall. However, on multivariable analysis, only infection status prior to HSCT was shown to be significant. In terms of overall clinical benefit, while the evidence

identified for inclusion in this review predominantly relates to survival, it is plausible that the findings may underrepresent the potential morbidity benefits in those who survive; such benefits may accrue from earlier treatment for SCID resulting in the sequelae of severe or frequent infection being reduced.

While age is frequently cited as a significant factor in the success of treatment, it is possible that age represents a proxy for the clinical condition, including infection status, of the child before treatment.[82, 137] Two of the studies reported that the majority of deaths (between 76% and 100% per study) were a result of infectious complications,[133, 170] and seven of the studies also reported that pre-HSCT infection negatively impacted survival outcomes.[118, 121, 122, 131, 136, 172, 175] It may be the case that timing of diagnosis and timing of HSCT are in fact a proxy for infection status, and that the infection status of the infant has the largest impact on survival. An infant with an earlier diagnosis and or transplant is less likely to have been exposed to and incurred infections than an infant diagnosed and receiving HSCT at an older age. Of note, one study reported that, unlike those from the early diagnosis group, infants from the late diagnosis group would not have received prophylactic antibiotics or immunoglobulin replacement therapy and this would have contributed to their higher rate of infectious complications.[170]

As noted in chapter two and chapter three of this report, specifically in the case of ADA-SCID, additional treatment options exist in terms of a bridging therapy (that is, enzyme replacement therapy) and curative intervention (that is, gene therapy). In the case of gene therapy, this treatment option was not considered within this chapter for a number of reasons. Firstly, HSCT remains the primary treatment for ADA-SCID (with specific consideration of donor type). Secondly, while a limited number of Irish children with ADA-SCID have been treated with gene therapy, this was only within the context of a clinical trial. Lastly, given that screening for ADA-SCID is under implementation at present in Ireland, the consideration of the treatment options for this form of SCID specifically was not identified as a core consideration of this HTA.

Although the international evidence broadly supports the use of early HSCT compared with late HSCT, there are a number of limitations that should be considered in interpreting the findings of this systematic review. Firstly, despite including studies from the year 2000 onwards, much of the included study data were collected across multiple decades and extended as far back as the year 1968. This is a direct consequence of the rare and heterogeneous nature of SCID which requires researchers to collate data over extended periods of time to ensure sufficient sample coverage for conducting study analysis. However, clinical data from several previous decades lack generalisability due to improvements in HSCT-related techniques and supportive care that have occurred over time. Secondly, three of the included

studies were based on clinical data of patients with SCID treated at Duke University Medical Center in the US.[133, 166-168, 173] As the data collection periods in these studies overlapped, it is likely that duplicate data is contained across the publications. Thirdly, this systematic review aimed to identify evidence evaluating the effectiveness of early diagnosis or HSCT compared with late diagnosis or HSCT. While the potential impact of infection status at HSCT has been discussed, other factors may also contribute to successful HSCT outcome, for example, individual patient characteristics, HSCT donor origin, the use of conditioning, and SCID subtype diagnosis; these factors were not accounted for in the studies presented within this review.

Considering the ideal evidence base for addressing the questions posed within this review, the clinical effectiveness of a health technology (for example, a screening programme, or a treatment) is typically evaluated using robust randomised controlled trials (RCTs) and high-quality observational studies. Owing to the process of randomisation that enables attribution of differences between groups based on the intervention evaluated, RCTs are considered the gold standard for examining cause-effect relationships between intervention and outcome.[178, 179] The design of an RCT to investigate the benefits of providing early HSCT compared with late HSCT for the treatment of children with SCID would neither be ethical (given the need for immediate specialist care and treatment) nor feasible (given the rare and heterogeneous nature of SCID) and therefore have not been conducted. In the absence of a randomised clinical trial, the most appropriate observational study design for identifying the independent effect of early versus late diagnosis and or HSCT would involve a cohort study carefully designed around assessing this association and removing the influence of confounding effects; amongst various important design elements, such a study would carry high internal validity through robust assessment of survival over a substantial follow-up period, and with careful design of a causation model adjusted for the many factors which might confound the association between exposure (early versus late diagnosis and or HSCT) and outcome (HSCT survival or other relevant clinical outcomes). Ideally also, such a study would be generalisable to the current Irish clinical context. Generally, retrospective cohort studies, provide useful clinical evidence to investigate rare outcomes. However, even the most carefully designed studies with access to comprehensive data are subject to sources of bias which make it difficult to obtain unbiased estimates of the effect of the exposure. In the present review, the design of the majority of the studies (n = 10) involved evaluating the impact of receiving early or late HSCT as part of a wider evaluation of a range of cohort characteristics, with the aim of establishing various factors that were associated with improved survival outcomes. These studies differ from cohort studies designed for the purpose of causal inference, in which the researcher sets out to directly examine and

compare the impact of the exposure (early diagnosis or HSCT) on patient-important outcomes. Nonetheless, the evidence generated by these studies, several of which performed robust survival analyses using large cohorts, provide useful insights into associations observed in these settings. While the body of evidence identified within the present review does not represent a rigorous body of evidence for a question of cause-and-effect, the evidence does suggest the presence of associations between early diagnosis and or HSCT and improved survival outcomes, with a consistent direction of association identified across almost all studies.

While the focus of this chapter was the direct benefits accruing to the child screened in terms of clinical outcomes, it is acknowledged that there may be additional benefits to the child, parent and family members in terms of early diagnosis and treatment, including the minimisation of the diagnostic odyssey and subsequent reduction of anxiety and stress. Such potential benefits should be balanced with potential harms that could be experienced by false positive results. An ongoing pilot evaluation of screening for SCID in the United Kingdom intends to consider such elements in terms of the impact of screening on the family; carers of children who had true negative, false positive, and true positive screening outcomes will be interviewed, along with the carers of children who were identified as having SCID, and other conditions, in the absence of screening.[58] However, the results of this evaluation are not expected until at least 2024.

Consideration of the patient and family experience, in the context of the early diagnosis and treatment of SCID, beyond clinical outcomes (for example, minimisation of the diagnostic odyssey and subsequent reduction of anxiety and stress) are discussed in chapter nine. Such potential benefits should be balanced with potential harms likely to be experienced by those with false positive results.

5.5 Conclusion

Overall, the international evidence generally suggests that early diagnosis and or HSCT in patients diagnosed with SCID is associated with improved clinical outcomes. However, study findings are limited by the observational nature of the evidence (which mainly comprised descriptive studies that investigated multiple factors associated with outcomes following HSCT), the lack of appropriate study design for investigating causation, the heterogeneous nature of the SCID study populations, and the applicability of the findings to the current clinical context in Ireland. Individual study findings were limited by the correlation of multiple factors that may influence HSCT outcomes, including infection status at HSCT, HSCT donor origin, the use of conditioning and SCID subtype diagnosis. Nonetheless, a consistent direction of association was observed within the identified studies, which represent the best available evidence for this question at this time.

6. Systematic review of the cost effectiveness of newborn screening for SCID

Key points

- A systematic review was undertaken to identify the available international evidence on the cost effectiveness of universal newborn screening for severe combined immunodeficiency (SCID), by way of T-cell receptor excision circles (TREC) quantification, compared with either no screening or with screening for ADA-SCID alone.
- No study was identified that compared universal screening for SCID with screening for ADA-SCID alone. Eleven independent studies were identified that evaluated the cost effectiveness of universal screening for SCID compared with no screening, targeted screening of infants with a family history of SCID, or identification through family history or clinical diagnosis. Ten of the studies were model-based, and one was based on empirical data from a pilot programme.
- Of the ten model-based studies, three performed a cost-utility analysis (CUA), three performed a cost-effectiveness analysis (CEA), and four studies presented results for both a CUA and a CEA. Eight of the model-based studies used decision trees and two used Markov models. The single study based on empirical data performed a CUA using a decision tree which was an update of one of the model-based studies using data from a pilot programme.
- To facilitate comparison across studies, the findings from the studies were reviewed in the context of willingness to pay (WTP) thresholds of €20,000 and €45,000 per quality adjusted life year (QALY) gained, which are typically used in Ireland as reference points for decision-making regarding the reimbursement of a technology.
- For CUAs, based on adjusted incremental cost-effectiveness ratios (ICERs), screening was considered potentially cost effective, at a WTP threshold of €45,000 per QALY gained, in six of seven studies.
- The study based on empirical data explored three TREC cut-off strategies, with all three ICERs at or below the WTP threshold of €45,000 per QALY gained.
- There was notable heterogeneity across the studies in terms of the inclusion of key variables such as the proportion of cases with a known family history, the

proportion of cases with ADA-SCID, and the impact of non-SCID T-cell lymphopenias.

- Through various sensitivity analyses, most studies reported that the models appeared to be sensitive to variations in a number of key variables, including: test specificity, incidence of SCID, screening test costs, diagnostic costs, the cost of treatment (especially costs of treatment for late detected SCID cases), and survival post treatment.
- Given the rarity of the condition, the relatively small birth cohort in Ireland, the treatment pathway (that is, HSCT takes place in the UK), and limitations in existing data, it is unlikely that there would be sufficient data available to support a model specific to the Irish context. Many of the parameter estimates to support such a model would need to be sourced from the studies included in this review, such as the UK, which would not reduce the uncertainty presented in the current review.
- Findings of the systematic review presented here represent the best available evidence for the cost effectiveness of the introduction of universal SCID screening to a newborn bloodspot screening programme. Considering the typical WTP thresholds used in Ireland, the majority of studies indicate that universal TREC-based screening for SCID, compared with no screening for SCID, is potentially cost effective. However, it should be noted that no study included a comparison of ADA-SCID screening.
- The current context in Ireland of universal ADA-SCID screening represents a relatively unique scenario and has implications for the evaluation of the cost effectiveness of screening for SCID.
    - In understanding the potential relevance of the results of this review, were screening for ADA-SCID in place, the incremental benefits would be expected to be lower as a proportion of the cases would already have been detected through such screening. However, the incremental costs would not be expected to be correspondingly lower. This would result in higher ICERs (that is, it would be less cost effective) than the estimates observed.
    - The cost effectiveness relative to a situation where ADA-SCID screening is in place (as is the case in Ireland) is unclear. Cost effectiveness depends in part on the number of cases that would be detected by TREC-based screening beyond those currently detected by ADA-SCID screening and detection based on family history. This is uncertain, in part due to the

potential for a population of cases that are currently undiagnosed (that is, those who may die prior to clinical presentation).

6.1 Introduction

As highlighted in chapters two and four, newborn screening for severe combined immunodeficiency (SCID) based on T-cell receptor excision circle (TREC) quantification has been implemented at a population level in a number of countries to date. The aim of this chapter was to summarise the available international evidence on the cost effectiveness of universal newborn screening for SCID compared with opportunistic detection (that is, detection on the basis of family history or clinical presentation), and to assess the applicability of the evidence to estimate the potential cost effectiveness of such a screening programme in Ireland.

6.2 Methodology

A protocol detailing the methods undertaken in this review has been published previously.[180] The reporting of this systematic review adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria.[181]

6.2.1 Review question

As part of scoping for this work, a search was undertaken to identify systematic reviews of the literature which investigated the cost effectiveness of universal newborn screening for SCID. No such systematic reviews were identified. Hence, a de novo review was undertaken for the following research question:

- What is the cost effectiveness of universal TREC-based newborn screening for SCID compared with no screening (or universal screening for ADA-SCID alone)?

The PICO (Population, Intervention, Comparator, Outcomes) framework used to formulate the research question is presented in Table 6.1. Screening for ADA-SCID (as implemented since May 2022) is important in the Irish context given the high prevalence of this form of SCID in the Irish population. This is a relatively unique scenario; as discussed in Section 2.5, only the Italian region of Tuscany, the region of Catalonia in Spain, and the US state of Michigan screen for ADA-SCID in addition to using TREC-based screening for SCID. Given this rarity, it was anticipated that there would be a lack of evidence comparing TREC-based screening with a scenario of ADA-SCID screening being in place. Therefore, it was also considered pragmatic to consider evidence of cost effectiveness of TREC-based screening compared with no screening.

Table 6.1 PICO framework for systematic review

Population	Children
Intervention	Universal TREC-based newborn screening for SCID
Comparator	▪ No newborn screening for SCID (with identification based on risk-based detection at birth or clinical presentation) ▪ Universal screening for ADA-SCID alone
Outcomes	ICER or NMB (for example, per life-year gained or quality-adjusted life-year)
Study design	Full economic evaluations: ▪ Cost-utility analysis ▪ Cost-effectiveness analysis

Key: ADA-SCID - adenosine deaminase deficiency severe combined immunodeficiency; ICER – incremental cost-effectiveness ratio; NMB – net monetary benefit; TREC – T-cell receptor excision circles; SCID – severe combined immunodeficiency

6.2.2 Types of studies

Economic evaluations can be considered partial (that is, costing studies in which only the cost of healthcare interventions are analysed) or full (that is, studies in which both costs and effects of two or more alternative strategies are compared).[182, 183] During scoping work completed to inform this review, it was noted that the majority of the economic analyses returned were in the form of cost-effectiveness analyses (CEA), cost-utility analyses (CUA) and simple costing studies.

In the interests of being able to assess the added value of the intervention relative to the cost, only full economic evaluations were considered relevant (that is, cost-utility analyses or cost-effectiveness analyses). Where other forms of cost analyses were identified, these were not included in this review, but were retained for later consideration in informing the budget impact analysis (see chapter 7).

6.2.3 Population of interest

The population of interest was newborns screened for SCID as part of a population-based programme.

6.2.4 Intervention and comparison of interest

The intervention of interest was universal TREC-based newborn screening for SCID with the comparators of interest being universal screening for ADA-SCID alone or no screening (with detection based on opportunistic means such as family history or clinical presentation).

6.2.5 Outcomes of interest

The primary outcome of interest was the incremental cost-effectiveness ratio (ICER), or net monetary benefit, of newborn screening for SCID compared with no screening, expressed in terms of cost per unit of health outcome gained. The preferred health outcome measure for this systematic review was the quality-adjusted life year (QALY), which was selected due to the ability of the QALY to summarise the quantity and quality of additional life years attributable to an intervention. Other outcomes (for example, cost per life years gained) were extracted where QALYs were not used as the measure of effect.

6.2.6 Exclusion criteria

The following exclusion criteria were applied:

- cost-benefit analysis, other types of cost analyses and comparative resource use studies
- commentaries, letters, conference papers and abstracts where a detailed description of the methods was not available.

6.2.7 Search Strategy

Electronic searches were conducted on 1 June 2022 in Medline (EBSCO), Embase (OVID) and the Cochrane Library, supplemented by a grey literature search literature including Google Scholar, national and health technology assessment (HTA) electronic sources up to 7 June 2022. Backward and forward citation searching of returned citations of relevance was also undertaken. The full search strategy was developed in consultation with a HIQA librarian and is presented in the supporting protocol.[180] Returned citations were imported to Covidence for reference management.

6.2.8 Study selection and data extraction

Study selection

Titles and abstracts of returned citations were screened independently by two reviewers. The full texts of potentially eligible studies were retrieved and independently assessed for eligibility by two reviewers according to the criteria outlined in Table 6.1, with any disagreements being resolved by discussion and a third reviewer where required. Where necessary, studies not available in the English language were translated using Google Translate.

Data extraction

A data extraction form was developed and piloted. Data were extracted by one reviewer and cross-checked in full by a second with any disagreements resolved through discussion and a third reviewer.

6.2.9 Data synthesis

In line with best practice recommendations, the results of model-based (that is, data were synthesised from a number of sources) and empirical study-based (that is, economic evaluations based on a single trial or observational study) economic evaluations were synthesised separately.[183] Given the heterogeneity of studies in terms of population and healthcare system characteristics, and in line with previous assessments on this topic conducted internationally,[77, 82] results were synthesised narratively.

To facilitate comparison of results across countries and years, where appropriate, costs were converted to Irish Euro in accordance with national HTA guidelines.[184] Briefly, the consumer price index for health from each country was used to inflate prices to 2021 value and the 2021 purchasing power parity was used to convert these values to Irish Euro (date of data download: 21 June 2022). Where different versions of a study were retrieved, only the results of the most recent update were presented. Willingness-to-pay (WTP) thresholds of €20,000 and €45,000 per QALY gained are typically used in Ireland as reference points for decision-making regarding the reimbursement of medicines.[185] Therefore, both thresholds were used for comparisons across studies in terms of the interpretation of the results from the CUAs for the Irish context.

6.2.10 Assessment of quality appraisal and applicability

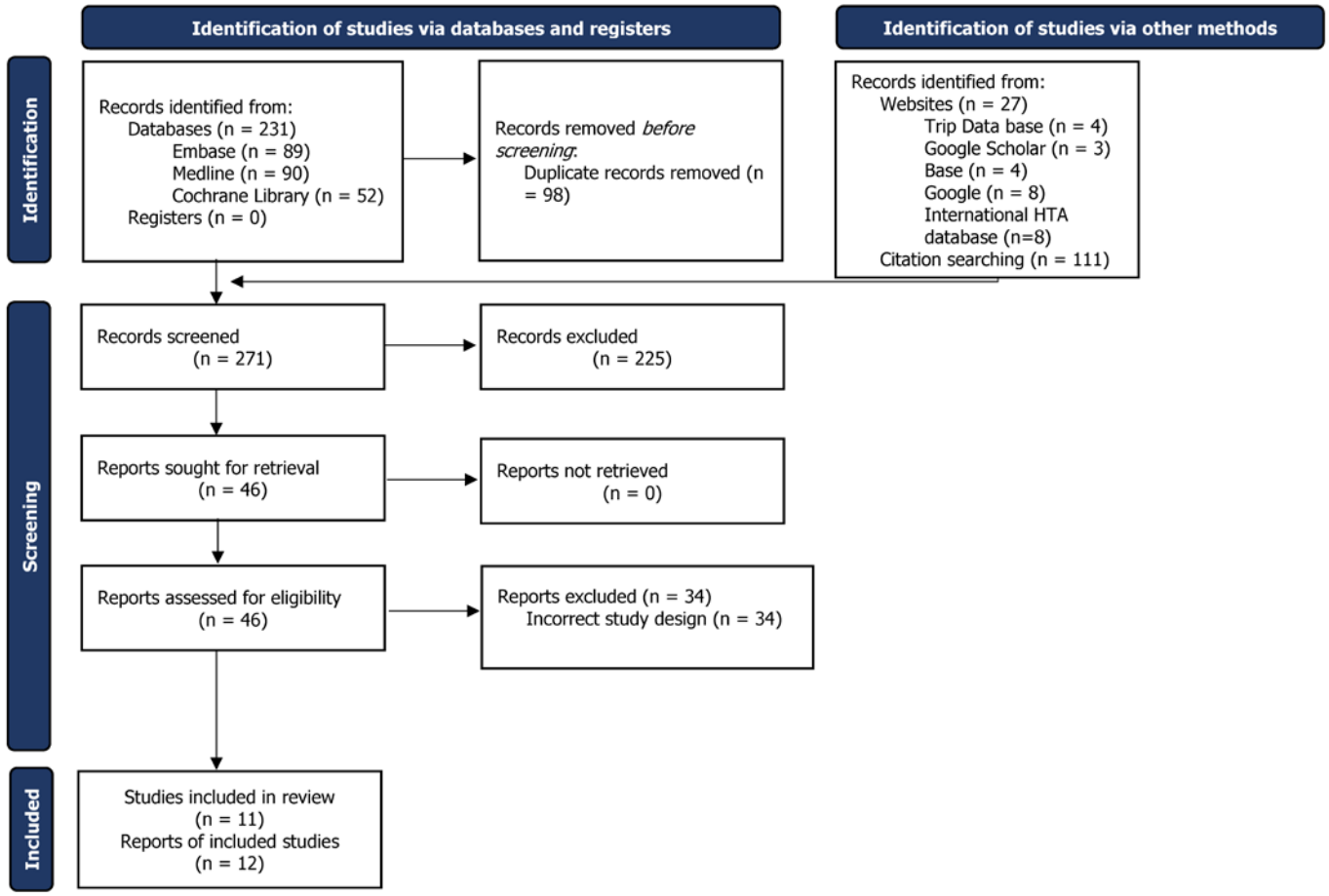
Assessment of the methodological quality of included studies was conducted using the Consensus on Health Economics Criteria (CHEC)-list.[186] The International Society for Pharmacoeconomics and Outcomes Research (ISPOR) questionnaire was used to assess the applicability of individual study findings to the Irish setting.[187] Criteria for each tool were defined and piloted between reviewers. Each assessment was performed by two reviewers independently with any disagreement resolved through discussion and the involvement of a third reviewer, where necessary. Validated methods for the numerical grading of studies for each tool were not identified and therefore the results of these assessments are presented based on the judgement of the reviewers.

6.3 Results

6.3.1 Search results

The PRISMA flow diagram, outlining the flow of information during the systematic review process, is presented in Figure 6.1. Overall, a total of 369 citations were retrieved from the search strategy. Of these, 98 were removed as duplicate citations. A further 225 were excluded following title and abstract screening with 46 being included in full text review. After completion of full-text review, 12 publications were identified that met the systematic review's eligibility criteria and were included in the synthesis.[101, 188-198] Two of the papers from the UK were considered to be linked updates (that is, the papers were largely based on the same data sources with minor adjustments in the estimates) published in 2017 as part of an evidence review to inform policy and subsequently as an academic publication in 2019.[101, 189] Only the later academic publication was included; however, where necessary, additional information was sought from the original assessment. Therefore, 11 independent studies were included in the synthesis overall.[101, 188, 190-198]

Figure 6.1 PRISMA flow diagram for review



6.3.2 Study characteristics

Ten of the included economic evaluations (including the two linked publications) were model-based analyses.[101, 188, 190-195, 197, 198] One study was an update of another included model-based analysis, [197] using empirical data from a pilot study in the Netherlands.[196]

6.3.2.1 Studies based on models

Of the ten model-based studies, three were conducted in the United States[188, 190, 193] (one specifically in the State of Washington),[190] and one each in New Zealand,[194] Canada (specifically in the province of Alberta),[192] Sweden,[198] the UK,[101] the Netherlands,[197] Finland,[191] and Spain.[195]

All of the ten model-based studies considered universal screening for SCID as the intervention of interest.[101, 188, 190-195, 197] Eight of the studies specifically stated TREC-based testing as the screening modality,[101, 188, 190, 191, 194, 195, 197, 198] one was presumed to be TREC-based due to explanations provided in other sections of the report, though this was not explicitly clear for the economic evaluation section,[192] and one study used a hypothetical test which had similar properties to a TREC-based test (given the year of the study, commercial TREC tests were not yet established).[193] The study that was presumed to be TREC-based explored screening for SCID independently, or as a combination with up to seven conditions for consideration to be added to the newborn bloodspot screening (NBS) programme in Alberta Canada, and it was not clear if the TREC test was performed in isolation or with the addition of kappa-deleting recombination excision circles (KREC).

The comparator was 'no screening for SCID' in eight of the model-based studies.[101, 188, 190-192, 194, 195, 197] One study stated that the comparator was targeted screening of infants with a family history of SCID,[193] and one stated the comparator was identification through family history or clinical diagnosis.[198]

6.3.2.1.1 Modelling approach

Of the ten model-based studies, three performed a CUA,[101, 193, 197] three performed a CEA,[190, 192, 194] and four studies presented results for both a CUA and a CEA.[188, 191, 195, 198] Details of the models are outlined in Table 6.2 and further described below.

Analysis type and model structure

Eight of the model-based studies used decision trees.[101, 188, 190, 193-195, 197, 198] Two studies included Markov models,[188, 192] one of which was a hybrid decision tree and

Markov model.[188] Three models adapted models from other contexts.[191, 195, 197] One study was not clear about the model type, however the report noted that there was tailoring of a model previously developed by American and Dutch researchers.[191] The study from the Netherlands stated that their model was an extension of a previous model from the United States,[190] which was adapted to the planned screening strategy for a pilot study on newborn screening for SCID in the Netherlands.[197] The study from Spain stated that the same model as that presented for the UK was used (a decision tree),[101] and adapted to the Spanish context.[195]

The study that included both a Markov model and a decision tree used the Markov models to characterise the populations in the decision tree.[188] The transition probabilities of the between states in the Markov model were obtained from medical literature, a national marrow donor registry, and survey of parents of children diagnosed with SCID, along with a review of a subset of the children's medical charts. The other study that included a Markov model considered the cost effectiveness of SCID screening in isolation or in combination with seven conditions; however, each condition, including SCID, was modelled separately.[192]

Perspective

Of the ten model-based studies, nine adopted a healthcare system perspective (two of which were from the US),[101, 190-195, 197, 198], and two adopted a societal perspective.[188, 198] The study from Sweden adopted both healthcare system and societal perspectives in separate analyses.[198]

Discount rate

Discounting reflects a societal preference for benefits to be realised in the present and costs to be experienced in the future. Discounting facilitates comparison between costs and benefits that occur at different times. Discount rates were reported in nine of the ten model-based studies.[101, 188, 190, 192-195, 197, 198] The discount rates included in the base-case analyses were 3%,[188, 190, 193, 195, 197, 198] 3.5%,[101, 194] and 5%.[192] Costs and benefits were discounted at the same rate in all studies. A number of included studies further considered varying discount rates within sensitivity analyses.

Time horizon

Seven of the model-based studies reported the modelled time horizon.[101, 188, 190, 192, 195, 197, 198] The time horizons included were lifetime (n = 5),[101, 192, 195, 197, 198], 70 years (n = 1),[188] and one study used five years for outcomes and lifetime for survival.[190] To note, estimates of life expectancy varied between studies (see Table 6.2).

Outcomes

All ten of the model-based studies provided outcomes in the form of ICERs.[101, 188, 190-195, 197] Six of the studies provided ICERs for cost per life year (LY) gained with screening, [188, 190-192, 194, 198] and seven provided ICERs for cost per QALY gained with screening. [101, 188, 191, 193, 195, 197, 198] The study from Spain presented five separate base cases in its analyses citing high uncertainty in estimates of the incidence of SCID and test cost.[195] For the purposes of the current review, the highest and lowest reported ICERs per QALY and ICERs per LY gained are presented.

Table 6.2 Characteristics of model-based studies

Author Country	Intervention	Comparator	Type of analysis	Model type	Perspective	Time horizon	Discount	Currency
McGhee 2005[193] United States	Universal screening for SCID (hypothetical test)	Targeted screening (screening only those infants with a family history of the disease)	CUA	Decision tree	Healthcare system	NR	3%	2000 USD
Chan 2011[188] United States	Universal screening for SCID (TREC-based test)	No screening for SCID	CUA and CEA	Decision tree; Markov model	Societal	70 years	3%	2005 USD
New Zealand Screening Unit 2014[194] New Zealand	Universal screening for SCID (TREC-based test)	No screening for SCID	CEA	Decision tree	Healthcare system (public health funder)	NR	3.5%	2013/2014 prices, assumed NZD
The Institute of Health Economics 2016[192] Alberta (Canada)	Universal screening for SCID (TREC-based test). Screened independently or in combination with other conditions.	No screening for SCID (in isolation or in conjunction with any of the other outlined conditions)	CEA	Markov model*	Healthcare system	Lifetime (birth to 80 years)	5%	2015 CAD
Ding 2016[190] Washington (United States)	Universal screening for SCID (TREC-based test)	No screening for SCID	CEA	Decision tree	Healthcare system	5 years (outcomes) Lifetime (survival)	3%	2012 USD
The National Board of Health and Welfare 2019[198] Sweden	Universal screening for SCID (TREC-based test)	Identification through family history or clinical diagnosis	CUA and CEA	Decision tree	Societal and healthcare system	Lifetime (0 to 90 years)	3%	2017 SEK

Bessey 2019[101] United Kingdom	Universal screening for SCID (TREC-based test)	No screening for SCID	CUA	Decision tree	Healthcare system (NHS and personal social services)	Lifetime	3.5%	2014/2015 GBP
van der Ploeg 2019[197] Netherlands	Universal screening for SCID (TREC-based test)	No screening for SCID	CUA	Decision tree; Extension of model by Ding; adapted to the planned screening strategy for a pilot study on newborn screening for SCID in the Netherlands	Healthcare system	Lifetime	3%	2016 Euro
Palko 2020[191] Finland	Universal screening for SCID (TREC-based test)	No screening for SCID	CEA (CUA included in sensitivity analysis)	Unclear design. Study cites tailoring of model previously developed by American and Dutch researchers	Healthcare system	NR	NR	2020 Euro
SESCS 2020[195] Spain	Universal screening for SCID (TREC-based test)	No screening for SCID	CUA and CEA	Decision tree; (adaptation of model used by Bessey)	Healthcare system	Lifetime (100 years maximum)	3%	2019 Euro

Key: CAD – Canadian dollar; CBA - Cost benefit analysis, CEA - Cost effectiveness analysis CUA - Cost utility analysis, GBP – pound sterling; NR - Not reported; RWD – real world data; SCID – severe combined immunodeficiency disease; SESCS - Servicio de Evaluación del Servicio Canario de la Salud; SEK – Swedish krona; TREC - T- cell receptor excision circle assay; USD – United States dollar.

* Screened independently or in combination with other conditions. Only the addition of SCID singularly was considered for this report. TREC-based testing was not explicitly stated.

6.3.2.1.2 Input parameters

The key input parameters for the model-based studies are outlined in Table 6.3 and described in detail below. A complete summary of included model parameters per study is detailed in Appendix 6.1.

Incidence

The base-case estimate of the incidence of SCID was stated in all ten model-based studies.[101, 188, 190-195, 197, 198] The base-case incidence ranged from 1:104,215 in the study from New Zealand[194] to 1:49,000 in the study from the UK.[101] Four studies included an incidence of SCID of 1:58,000 in the base case analysis.[190-192, 197] A Spanish evaluation stated that two incidences were explored in the base-case analyses; 1:50,000 and 1:60,000.[195] Two studies included the proportion of SCID cases that were ADA-SCID, with both using a proportion estimate of 0.17.[101, 195]

The incidence of non-SCID TCLs was included in six of the ten model-based studies.[101, 190-192, 195, 197] Two of these six studies included the incidence categorised as 'other syndromes', 'secondary disease', and 'idiopathic TCL'.[101, 195] The other four studies did not separate the non-SCID TCLs; the incidence in the base case was 1:14,000 in three of these studies,[190, 191, 197] and was 1:11,434 in the remaining study.[192]

Costs

The TREC test cost was reported in eight of the ten model-based studies,[101, 188, 190, 191, 194, 195, 197, 198] with the remaining two studies reporting the incremental cost of adding testing for SCID to the current screening programme.[192, 193] Components of the test cost (range: €3.12 to €6.37) often included the consumables, the labour, and the laboratory equipment. However, some studies did not report the included components of the cost, or included just the price of the assay itself, with components such as labour listed as a separate model input.

While all the ten model-based studies reported on some inputs for treatment cost, overall, the components were poorly reported, with much heterogeneity between the included costs.[101, 188, 190-195, 197, 198] Two studies reported the treatment cost for all SCID cases,[193, 195] with one explicitly stating that the given cost was for HSCT.[195] The remaining seven studies provided separate costs for when SCID was detected early (range: €65,826 [including HSCT and post-HSCT support, which were listed separately] to €277,876 [additionally including medical expenses before transplant and medical expenses after transplant, which were listed separately]) and when SCID was detected late (range: €191,209 to €441,772).[101, 188, 190-192, 194, 197, 198]

Overall, it was unclear what was included in each of the provided costs (meaning whether just the cost of the HSCT itself was included, or whether additional cost components such as pre- or post-HSCT hospitalisations and post-HSCT support were also included).

Utility values

Seven of the ten model-based studies included utility values, with a variety of methods used to estimate these values.[101, 188, 191, 193, 195, 197, 198] The utility values used in the models are outlined in Appendix 6.1.

- One study from the US estimated health preference scores based on literature from studies of bone marrow transplant patients for oncologic disease (of note, it was unclear whether the patients referred to were children or adults, or both), and provided separate estimates for those described as having a 'successful HSCT' and for those described as needing ongoing intravenous immunoglobulin (IVIG) therapy following HSCT.[193]

- Another study from the US estimated utility values for children with SCID after HSCT by averaging published utilities for children with cystic fibrosis, sickle cell anaemia, paediatric HIV-AIDS, medium chain acyl CoA dehydrogenase deficiency, and leukaemia.[188] This study did not appear to use different utility values dependent on the outcome of the HSCT, or whether the SCID was detected early versus late.

- A study from the UK obtained utility values by mapping information from a database of UK SCID patients transplanted between 1979 and 2015 onto the EQ-5D-3L health state descriptions.[101] The average health state utility for patients diagnosed at birth and patients diagnosed later were provided. In order to explore the effect of improved treatment over the time period, a sensitivity analysis was conducted with estimates of patients transplanted between 2000 and 2015.

- A study from the Netherlands estimated utilities in consultation with clinical experts, and defined three different possibilities: a good health status, in which an average age of 65 years is reached in a good quality of life (alive and well with no need for further surgery or immunoglobulin treatment); a moderate health status, in which an average age of 40 years is reached in moderate quality of life (either alive and well with immunoglobulin therapy, alive with clinical symptoms without immunoglobulin therapy, or alive with clinical symptoms with immunoglobulin therapy); and a poor health status, in which an average age of 25 years is reached in a lesser quality of life (alive

with sequelae without immunoglobulin therapy or with immunoglobulin therapy).[197]

- A study from Finland stated that utilities were from expert judgement based on values from the Netherlands study above,[197] without providing any further details.[191] These utility values were used only in a sensitivity analysis, and not as part of base-case analyses.

- The study from Spain stated that the utility values from the UK study above,[101] were used.[195]

- Finally, the study from Sweden was not clear as to how the values were estimated, however the study from the UK[189] was referenced, indicating that the UK values may have been used.[198]

Additional considerations

Four studies explicitly included the costs associated with non-SCID TCLs detected by screening, additional to those costs incurred during diagnosis.[101, 192, 195, 197]

- The study from the UK included the incremental costs associated with the non-SCID TCLs detected via screening (such as immunology appointments) rather than symptomatically, as well as costs for longer-term follow-up for those in which screening would enable an earlier diagnosis, and those who may not have presented symptomatically.[101] It was not clear what the incremental and longer-term follow-up costs comprised, for example, if the management of the disease was included.

- The study from the Netherlands included the cost of treatment for non-SCID TCLs per type: transient, idiopathic, and other.[197] This study assumed in their base case that children with non-SCID TCLs would have been identified with or without screening and would incur the same treatment costs regardless of whether screening was in place or not. However, a sensitivity analysis was also conducted, which assumed that children with non-SCID TCL would not be detected in a situation without screening.

- The study from Spain included costs associated with follow-up, including specialist visits, genetic tests, and flow cytometry, of other syndromes and of other secondary diseases.[195]

- The study from Canada included syndromes with T-cell impairment, secondary T-cell impairment, and variant SCID in their modelling to capture the costs and resources of monitoring these conditions that would otherwise

not have been identified in the absence of screening.[192] It was not clear what the costs of monitoring the conditions comprised, such as whether confirmation of diagnosis and management of the disease were included.

One study included an estimate of the incidence of undiagnosed SCID. This study, from the UK, estimated an incidence of undiagnosed SCID of 1:521,000 (95% CI: 1:167,052 to 1:7,236,800), although this estimate was associated with high uncertainty as indicated by the wide confidence intervals.[101]

Table 6.3 Key input parameters for model-based studies

Author Country	Incidence of SCID (range) Proportion ADA-SCID	Incidence of non-SCID TCLs (range)	TREC test adjusted* cost (range) Components of test cost	Treatment adjusted* cost (range)
McGhee 2005[193] United States	1:50,000 (1:30,000 to 1:1,000,000) NR	Not included	NR (incremental cost of introducing the hypothetical SCID test into existing NBS panel using DBS and current reporting stream: €7.81 (€3.12 to €101.54))	Treatment cost – €98,598. (€31,244 to €1,562,175)**
Chan 2011[188] United States	1:75,000 (1:25,000 to 1:500,000) NR	Not included	€5.32 (€0.63 to €37.81) Machine usage, labour, and reagents	Cost ratio for HSCT when SCID detected early vs. SCID detected late of 1:3 (0.50 to 10)
New Zealand Screening Unit 2014[194] New Zealand	1:104,215 (0:60,000 to 1.74:60,000) NR	Not included	€3.12 Reagent, labour, laboratory overhead	Cost when SCID detected early ▪ HSCT – €41,993 ▪ Post-HSCT support – €23,833 Cost when SCID detected late ▪ Treatment excluding HSCT – €84,515 ▪ Treatment including HSCT – €152,516 ▪ Additional HSCT – €94,185 ▪ post-HSCT support – €23,833
The Institute of Health Economics 2016[192] Alberta (Canada)	1:58,000 (1:100,000-2:58,000) NR	1:11,434	NR (incremental cost of adding SCID to current screening programme including	Cost when SCID detected early ▪ Hospitalisation, HSCT – €53,581 ▪ Physician, HSCT – €4,286.52 ▪ Hospitalisation, post-treatment management – €25,914 ▪ Physician, post-transplant management –

			equipment, labour and supplies: €9.84)	€2,076 Costs when SCID is detected late ▪ Hospitalisation, HSCT – €160,744 ▪ Physician, HSCT – €4,287 ▪ Hospitalisation, post-treatment management – €77,741 ▪ Physician, post-transplant management – €6,219
Ding 2016[190] Washington (United States)	1:58,000 (1:46,000 to 1:80,000) NR	1:14,000 (1:11,600 to 1:16,400)	€3.97 (€2.95 to €5.89) laboratory test for TREC assay	Cost of treatment in patients who receive HSCT as first-line therapy when SCID detected early – €98,172 (€78,537 to €117,806) Cost of treatment in patients who receive HSCT as first-line therapy when SCID detected late – €441,772 (€294,515 to €1,178,058) Cost of treatment in patients with ADA-SCID who do not undergo early HSCT – €441,772 (€196,343 to €736,286)
The National Board of Health and Welfare 2019[198] Sweden	1:50,000 (1:37,000 to 1:20,000) NR	Not included	€5.40 testing of blood	Cost when SCID detected early** ▪ Medical expenses before transplant – €95,776 ▪ Medical expenses after transplant – €182,100 Cost when SCID detected late** ▪ Medical expenses before transplant – €150,334 ▪ Medical expenses after transplant – €239,683
Bessey 2019[101] United Kingdom	1:49,000 (1:39,857 to 1:61,527) 0.17 (0.1 to 0.26)	Incidence of other syndromes: 1:45,000 (1:24,390 to 1:110,606) Incidence of secondary	€4.64 (€1.99 to €5.96) screening test kit	Cost of HSCT when SCID detected early – €170,128 Cost of HSCT when SCID detected late – €306,407

		conditions 1:130,000 (1:50,686 to 1:782,506) Incidence of idiopathic TCL 1:99,000 (1:42,255 to 1:432,482)		
van der Ploeg 2019[197] Netherlands	1:58,000 (1:46,000 to 1:80,000) NR	1:14,000 (1:8,200 to 1:16,400)	€5.18 (€3.85 to €6.05) test, analytical support, maintenance, and depreciation costs	Cost of HSCT when SCID detected early – €98,999 (€82,499 to €137,499) Cost of HSCT when SCID detected late – €225,498 (€164,998 to €494,995)
Palko 2020[191] Finland	1:58,000 (1:80,000 to 1:46,000) NR	1:14,000 (1:16,400 to 1:8,200)	€3.78 (€0 to €5.68) NR (noted as part of NBS)	Cost of HSCT when SCID detected early – €84,169 Cost of HSCT when SCID detected late – €191,209
SESCS 2020[195] Spain****	1:50,000 and 1:60,000 0.17	Incidence of other syndromes - 1:32,500 Incidence of secondary diseases - 1:130,000 Incidence of idiopathic TCL - 1:65,000	€6.37 (€3.82 to €12.75) calibration, initial TREC estimation, and beta-actin estimation	Cost of HSCT – €95,808***

Key: ADA - Adenosine deaminase; DBS – dried blood spot; HSCT – hematopoietic stem-cell transplantation; NBS – newborn screening; NR – not reported; SESCS - Servicio de Evaluación del Servicio Canario de la Salud; SCID – severe combined immunodeficiency disease; TCL – T cell lymphopenia; TREC - T-cell receptor excision circle assay.

* Results were adjusted to 2021 Irish Euro using consumer price indices and purchasing power parity estimates.

** Unclear whether HSCT is included in these costs.

*** Treatment costs were not given for early versus late treatment separately

**** Given high uncertainty in two key parameters (SCID incidence and test cost), the authors cite multiple base cases were considered varying the incidence from 1:50,000 to 1:60,000 and the test cost to €5.10, €6.37 or €7.65

6.3.2.2 Study based on empirical data

The single study based on empirical data was an update of the previously described model-based study from the Netherlands,[197] using real-world data from a pilot programme.[196] Details of the model are outlined in Table 6.2 and key input parameters for the study are outlined in Table 6.3. Additional model parameters are detailed in Appendix 6.1.

The pilot programme was a prospective implementation study of the inclusion of SCID screening by TREC to the current NBS programme in three of 12 provinces. The study was a CUA using decision trees. Outcomes were presented in terms of ICERs per QALY gained. The study used a healthcare system perspective, a lifetime time horizon, and a 3% discount rate.

Three TREC cut off-values for referral strategies were explored;

- Strategy 1: TREC ≤ 6 copies/3.2 mm,
- Strategy 2: TREC ≤ 10 copies/3.2 mm,
- Strategy 3: direct referral if TREC levels ≤ 2 copies/3.2, and cases with TREC-levels > 2 to ≤10 require a second heel prick after seven days.

The study included an incidence of SCID of 1:58,000.[196] The incidence of non-SCID TCLs was 1:3,974 for Strategy 1, 1:2,493 for Strategy 2, and 1:4,710 for Strategy 3. The adjusted cost of the TREC test was €6.56, and this included the TREC assay, use of laboratory equipment, and material and personnel. The cost of HSCT when SCID was detected early and the cost of HSCT when SCID was detected late were both included in the parameters.

Table 6.4 Characteristics of study based on empirical data

Author Country	Intervention	Comparator	Type of analysis	Model type	Perspective	Time horizon	Discount	Currency
van den Akker-van Marle 2021[196] Netherlands	Universal screening for SCID (TREC-based test)	No screening for SCID	CUA	Update on Van der Ploeg et al. decision-tree model above using RWD from a pilot study	Healthcare system	Lifetime	3%	2020 Euro

Key: CUA - Cost utility analysis, RWD – real world data, SCID – severe combined immunodeficiency disease , TREC - T- cell receptor excision circle assay

Table 6.5 Key input parameters for empirical-based study

Author, Country	Incidence of SCID (range) Proportion ADA-SCID	Incidence of non-SCID TCLs (range)	TREC test adjusted* cost (range) Components of test cost	Early versus late treatment adjusted* cost (range)
van den Akker-van Marle 2021[196] Netherlands	1:58,000 NR	TREC ≤ 6 Copies/3.2 mm - 1:3,974 TREC ≤ 10 Copies/3.2 mm - 1:2,493 Direct referral if TREC levels ≤ 2 copies/3.2 , and cases with TREC-levels > 2 to ≤10 require a second heel prick after seven days, respectively - 1:4,710	€6.56 TREC assay, use of laboratory equipment, and material and personnel	Cost of HSCT when SCID detected early: €92,870 Cost of HSCT when SCID detected late: €211,538

Key: ADA - Adenosine deaminase, HSCT – hematopoietic stem-cell transplantation, SCID – severe combined immunodeficiency disease , TCL – T cell lymphopenia, TREC - T-cell receptor excision circle assay

* Results were adjusted to 2021 Irish Euro using consumer price indices and purchasing power parity estimates.

6.3.3 Summary of findings

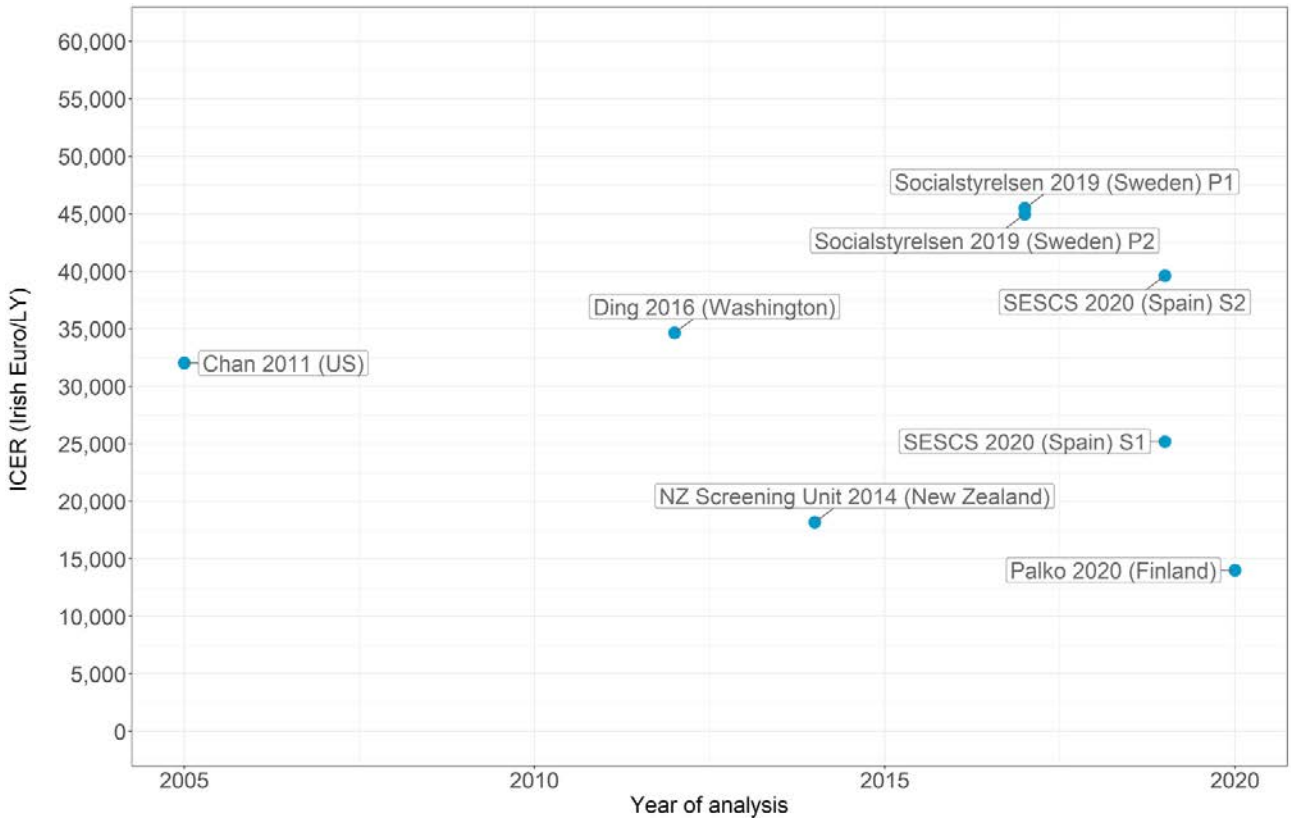
A summary of the key findings, including the key cost outcomes and ICERs, is described below. The results from the studies based on models (Table 6.6) and the results from the study based on a trial (Table 6.7) are described separately. Additionally, the results are presented separately depending on whether ICERs were provided in terms of LYs or QALYs. A summary of the sensitivity analyses is also presented (Table 6.8). The key outcomes and ICERs are presented without cost adjustments (that is, the currency and cost year reported in each individual study) in Appendices 6.2 and 6.3.

6.3.3.1 Studies based on models

Cost per life years gained

Seven of the ten model-based studies provided ICERs for cost per LY gained with screening.[188, 190-192, 194, 195, 198] As shown in Figure 6.2, the adjusted ICERs differed substantially, ranging from €14,027/LY gained in the study from Finland,[191] to €217,657/LY gained in the study from Canada.[192] Of note, as previously stated in Table 6.2, the study from Canada explored the cost effectiveness of SCID screening versus no screening for SCID in isolation or as varying combinations with seven other conditions. Previous commentaries on this report have highlighted the delays in performing transplants in the region, in part due to lack of capacity, which may impact potential costs and benefits, and a failure to consider each of the individual conditions in sufficient detail.[77, 195] Excluding this study as an outlier, the upper range of the adjusted ICERs for studies using a healthcare payer perspective was €45,516/LY gained. The studies reported various cost outcomes that were part of the cost-effectiveness analyses. These included 'the cost to identify and treat each additional case of SCID', the 'incremental cost per infant screened', 'annual costs of screening and diagnosis, as well as management of non-SCID cases', 'direct medical costs associated with screening', and 'lifetime cost of programme' and are presented in Table 6.6.

Figure 6.2 Adjusted ICERs per LY gained from model-based studies* (based on adjustments to 2021 Irish Euro)



Key: ICER – incremental cost effectiveness ratio, LY - life year, WTP - willingness-to-pay
Multiple perspectives were presented from Sweden with P1 being healthcare system perspective; P2 being societal perspective. Multiple base cases were presented for the study from Spain with highest and lowest values presented here with S1 – Situation in which the adjusted unit cost of the screening test is €5.10 and the incidence is 1:50,000. S2 – Situation in which the adjusted unit cost of the screening test is €7.65 and the incidence is 1:60,000.
*Excludes outlier value from The Institute of Health Economics 2016[192]

Cost per quality-adjusted life years gained

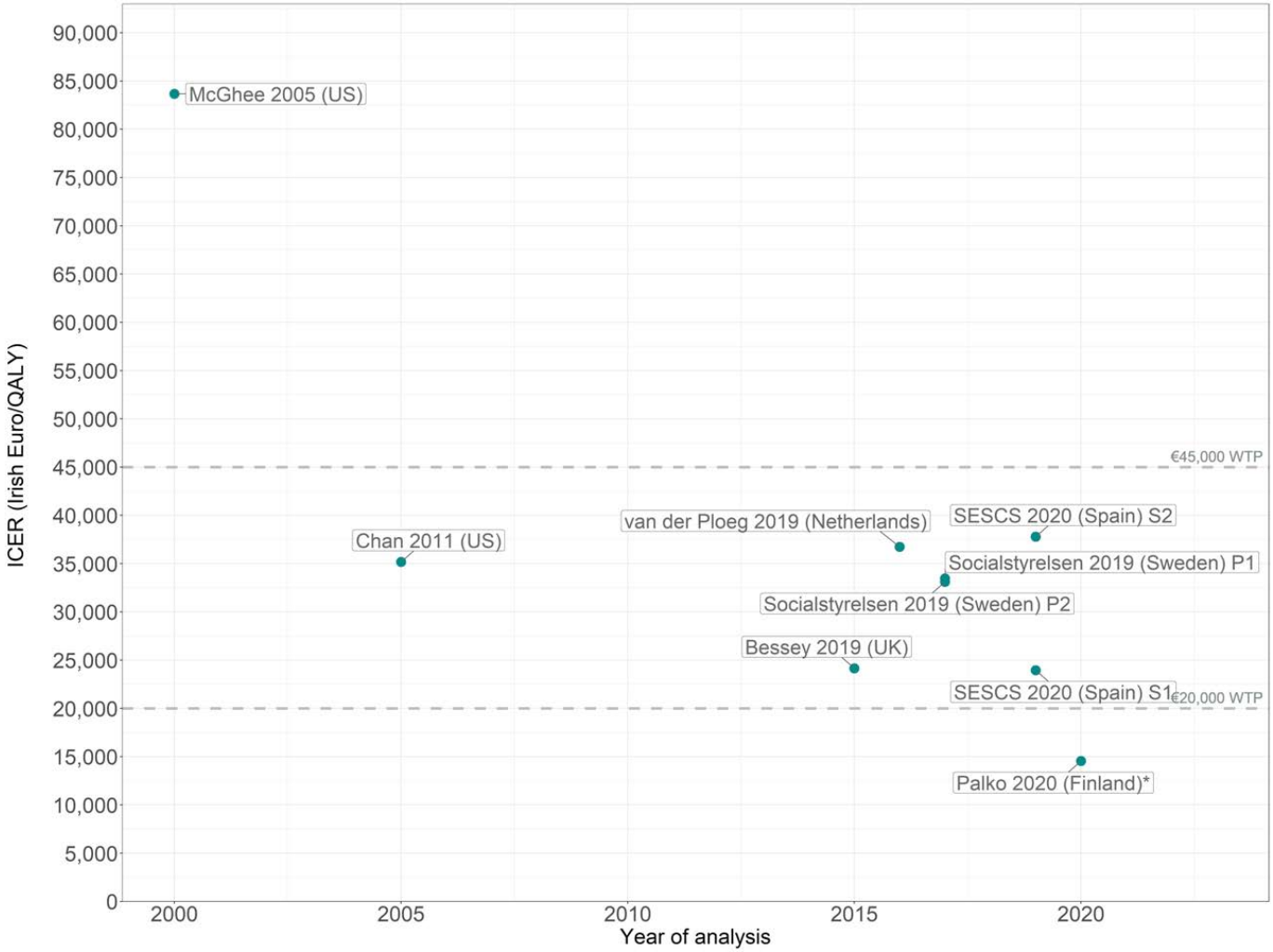
Seven of the ten model-based studies provided ICERs for cost per QALY gained with screening.[101, 188, 191, 193, 195, 197, 198] As shown in Figure 6.3, the adjusted ICERs ranged from €14,549/QALY in the study from Finland [191] to €83,670/QALY in one study from the US.[193] The study from Finland calculated ICERs based on QALYs in sensitivity analyses; however, this was not part of the base case analysis.[191] The study from the US (published in 2005) was based on a hypothetical test for SCID which was not explicitly TREC-based.[193] Excluding these two studies, the adjusted ICERs ranged from €24,151/QALY in the study from the UK[101] to €35,169/QALY in another study from the US.[188]

Willingness to pay threshold in relation to Irish thresholds

As previously stated, WTP thresholds of €20,000 and €45,000 per QALY gained are typically used in Ireland as reference points for decision-making regarding the reimbursement of medicines.[185] Adjusted estimates from the included studies were compared against these reference points. (Figure 6.3).

Seven of the ten model-based studies provided ICERs for cost per QALY. [101, 188, 191, 193, 195, 197, 198] Six of these studies (nine analyses) reported ICERs below the WTP threshold of €45,000 per QALY (that is, the intervention would be considered potentially cost-effective in the Irish healthcare setting),[101, 188, 191, 195, 197, 198] with the ICER in one study below the WTP threshold of €20,000 per QALY (that is, the intervention would be considered cost effective).[191] The only study providing an ICER above the threshold of €45,000 per QALY was a study from the US; it was based on a hypothetical test for SCID which was not explicitly TREC-based, and was published in 2005.[193]

Figure 6.3 Adjusted ICERs per QALY gained from model-based studies (based on adjustments to 2021 Irish Euro)



Key: ICER: incremental cost effectiveness ratio, QALY: quality-adjusted life year, WTP: willingness-to-pay

* The study from Finland calculated ICERs for QALYs in sensitivity analyses, however this was not part of the base case analysis

Note: Multiple base cases were presented for the study from Spain with highest and lowest values presented here with S1 – Situation in which the adjusted unit cost of the screening test is €5.10 and the incidence is 1:50,000. S2 – Situation in which the adjusted unit cost of the screening test is €7.65 and the incidence is 1:60,000.

Multiple perspectives were presented from Sweden with P1 being healthcare system perspective; P2 being societal perspective.

Table 6.6 Base-case results for model-based studies (adjusted to 2021 Irish Euro*)

Author Country	Adjusted Key Outcomes*	Adjusted ICER*
McGhee 2005[193] United States	▪ Cost to identify and treat each additional case of SCID - €757,655 ▪ Assuming birth cohort of four million per year, cost of implementing screening would be €37,367,228 and would result in 760 LY saved per year	▪ €83,670/QALY
Chan 2011[188] United States	▪ Implementation of screening for SCID with TREC would cost €28,229,104 with a gain of 880 LYs or 802 QALYs	▪ €32,046/LY ▪ €35,169/QALY
New Zealand Screening Unit 2014[194] New Zealand	▪ 'No screening' but with and relying on opportunistic clinical diagnosis, the cost is approximately €93,980 per year and gain of 4.1 LY ▪ Screening for SCID cost estimated at €275,293 per year, inclusive of treatment costs, with a gain of 14.0 LY. ▪ The net costs to the public health system in the presence of screening would be €181,313 per year and a gain of 10.0 LY.	▪ €18,192/LY
The Institute of Health Economics 2016[192] Alberta (Canada)	▪ Incremental cost of €9.10 per infant screened with 0.00004 LY gained when comparing screening with no screening	▪ €217,657/LY
Ding 2016[190] Washington (United States)	▪ Annual costs of screening and diagnosis, as well as management of non-SCID TCL cases - €8.01 per infant screened ▪ Net direct medical costs associated with screening of €416,709 (net considering 43% offset saving) with an additional 12.02 LY gained	▪ €34,665/LY
The National Board of Health and Welfare 2019[198] Sweden	▪ Annual cost to the society of no screening (current scenario of opportunities for early and late diagnosis and treatment) estimated at €989,487 for 31.7 QALYs/45.2 LYs gained. ▪ Annual cost to the society of screening estimated at €1,736,099 for 54.5 QALYs/62.0LYs gained. ▪ Additional annual cost to society of adding SCID to the NBS is estimated at €755,608 ▪ Annual cost to healthcare system of adding SCID to the NBS is estimated at €656,659.	Societal perspective: ▪ €44,977/LY ▪ €33,103/QALY Healthcare system perspective: ▪ €45,516/LY ▪ €33,463/QALY

Bessey 2019[101] United Kingdom	▪ Cost of screening estimated at €9,675,195 with 410.1 QALYs gained ▪ Cost of no screening estimated at €5,248,462 with 226.9 QALYs gained ▪ Incremental cost estimated at €4,426,733 with 183.17 QALYs gained	▪ €24,151 (€15,922 to €36,796)/QALY
van der Ploeg 2019[197] Netherlands	▪ Total healthcare costs without screening estimated at €583,324 per 100,000 infants ▪ Total healthcare costs with screening estimated at €1,013,199 per 100,000 infants ▪ Incremental healthcare costs estimated at €428,995 per 100,000 infants with 11.7 QALYs gained	▪ €36,740/QALY
Palko 2020[191] Finland	▪ Compared with no screening, SCID screening would cost an additional €170,304/year with 12.2 LY gained or 11.7 QALYs	▪ €14,027/ LY ▪ €14,549/QALY**
SESCS 2020[195] Spain	▪ Lifetime cost of programme for a cohort of 372,777 newborns: o Without screening ranges from €1,744,022 to €2,086,091 (depending on the incidence being 1:50,000 or 1:60,000) with 101 to 122 LYs or 87 to 105 QALYs o With screening ranges from €4,399,648 to €5,689,047 (depending on the incidence being 1:50,000 or 1:60,000 and the test cost being 5.10, 6.37, or 7.65) with 192 to 227 LYs or 183 to 215 QALYs gained o Incremental cost ranges from €2,655,624 to €3,602,956 with 91 to 105 LYs or 95 to 111 QALYs gained	▪ Range from €25,212/LY, if the unit cost of the screening test is €5.10 and the incidence is 1:50,000, to €39,634/LY if the unit cost of the screening test is €7.65 and the incidence is 1:60,000. ▪ Range from €23,951/QALY, if the unit cost of the screening test is €5.10 and the incidence is 1:50,000, to €37,788/QALY if the unit cost of the screening test is €7.65 and the incidence is 1:60,000.

Key: ICER – incremental cost-effectiveness ratio, LY – life-years, NBS – newborn screening, QALY – quality-adjusted life-year, SESCS - Servicio de Evaluación del Servicio Canario de la Salud, SCID – severe combined immunodeficiency disease, TREC - T cell receptor excision circle assay

* Results were adjusted to 2021 Irish Euro using consumer price indices and purchasing power parity estimates.

** When similar QALY estimates described by van der Ploeg et al (2019) were used in sensitivity analyses.

Sensitivity analysis

As outlined in Table 6.7, all ten model-based studies reported performing sensitivity analyses;[101, 188, 190-195, 197, 198] however, details of the type of analyses or results were unavailable for one of the studies (US-based).[193] Deterministic sensitivity analyses, including both one way and or two way sensitivity analyses, were performed in nine of the studies.[101, 188, 190-192, 194, 195, 197, 198] Probabilistic sensitivity analyses were performed in three of the studies.[101, 192, 195] One study performed a probabilistic scenario analysis applying variations in the means of the distribution functions of three key parameters (the discount rate, the cost of the screening test and the incidence of SCID), compared to a base case in which the discount applied to costs and benefits was 3%, the cost of the screening test was €5, and the incidence of SCID was 1:50,000.[195]

Overall results indicated that the models appeared to be sensitive to variations in the following key variables: test specificity, incidence of SCID, test and diagnostic costs, the cost of treatment (especially the difference in cost between early versus late treatment), and survival post treatment.[101, 188, 190-192, 194, 195, 197, 198] In contrast to most of the other studies, the study from Canada found no substantial impact of the incidence of SCID. Other variables that were found to have a potential impact were the discount rates,[194], the TREC cut-off,[101] the proportion of cases of SCID identified through family history,[101] and the percentage of infants requiring flow cytometry.[195, 197]

One study performed an expected value of perfect information (EVPI) analysis.[101] The key uncertainties in the single parameter EVPI analysis were the incidence of SCID and the length of stay in non-critical care for early HSCT. Additional uncertainties related to the relative survival benefit from early versus late HSCT, the proportion detected due to a family history, and the disbenefit experienced by non-SCID TCLs and false positive cases detected in screening.

Table 6.7 Key sensitivity analysis results in model-based studies*

Author Country	Type of analysis	Key Scenarios	Key results
McGhee 2005[193] United States	Sensitivity analysis (not specified)	▪ Likelihood of missing SCID case varied from 0 to 0.8 ▪ Evaluation of the model under circumstances in which transplantation cost only 23,423.63 and treatment of infection cost 1,562,175.08 ▪ Use of a wide range of survival times (10 to 79 years) ▪ Range of WTP thresholds	▪ NR
Chan 2011[188] United States	One way and two way sensitivity analysis	▪ Varying incidence, test sensitivity, test specificity, cost of TREC test, cost of diagnostic testing, and ratio of cost of early versus late HSCT ▪ Range of WTP thresholds	▪ Analyses indicated that screening test specificity and incidence were key drivers with costs of the screening test and diagnostic test also having an impact.
New Zealand Screening Unit 2014[194] New Zealand	One way sensitivity analysis	▪ Varying incidence rate, test costs, discount rates, and survival outcomes and treatment costs associated with early and late detection	▪ Analyses indicate that results are sensitive to incidence of SCID, life expectancy and discount rates, with cost of treatment having only a marginal impact.
The Institute of Health Economics 2016[192] Alberta (Canada)	One way and probabilistic sensitivity analysis (5,000 Monte Carlo simulations)	▪ Probabilistic sensitivity included varying disease sequelae, mortality rates and costs of diagnosis, treatment and overall management ▪ One way sensitivity analysis included varying incidence rates on number of cases detected and cost difference between early versus late HSCT	▪ One way sensitivity analyses did not indicate substantial impact of incidence; however varying HSCT cost differences between early and late detection had a considerable impact. ▪ Probabilistic sensitivity analyses indicate results are consistent and not overly sensitive to changing model assumptions.

Ding 2016[190] Washington (United States)	One way and two way sensitivity analysis	▪ Ranges of key variables including prevalence, sensitivity, specificity, cost of test, cost of treatment and survival.	▪ One way sensitivity analyses indicated that the upper-bound ICER estimate the willingness to pay threshold (defined by the study) for three variables subject to uncertainty: the probability of survival in late-identified SCID, cost per laboratory test, and the birth prevalence of SCID. ▪ The variable that had the greatest impact on the ICER, on the basis of one way analyses, was the treatment cost per late-identified infant with SCID who receives HSCT as first-line therapy; screening would be cost-saving if this variable was to exceed €950,889.43 ▪ Two way sensitivity analyses indicate that the influence of the treatment cost per late-identified infant with SCID who receives HSCT as first line therapy increases as the cumulative survival rate for infants with late-diagnosed SCID increases. ▪ If late diagnosis of SCID has a small effect on mortality, the ICER is influenced more by the relative treatment costs of late diagnosed versus early diagnosed cases
The National Board of Health and Welfare 2019[198] Sweden	Deterministic sensitivity analyses	▪ Ranges of key variables including cost of screening test, healthcare costs, incidence, and proportion of SCID cases offered early HSCT under a situation of no screening, and discount rates.	▪ Results were sensitive to a number of parameters, particularly for including the cost of the screening test and the discount rate used. The results were also sensitive to the incidence of SCID and difference in expected at survival for early versus late HSCT
Bessey 2019[101] United Kingdom	One-way and probabilistic sensitivity analysis EVPI analysis	▪ Varying proportion of SCID patients identified due to a family history in the no-screen arm, the cost of the screening test, incidence rates, and the discount rates ▪ Increasing TREC cut-off (increased presumptive positive cases assumed to be additional false-positive cases in the first instance and a proportional increase in the non-SCID TCL cases in the second)	▪ Results were sensitive to a number of parameters, including the cost of the screening test, the incidence of SCID, false positive cases, TREC cut-off (and subsequent detection of non-SCID TCLs) and proportion of cases of SCID identified through family history. ▪ EVPI analysis indicated that, assuming an annual number of births of 780,835 and a decision horizon of five years, the overall expected value of removing decision uncertainty for the United Kingdom was estimated at €789,787.49 o Key uncertainties in the single parameter EVPI analysis were the incidence of SCID and the length of stay in non-critical care for early HSCT. Further uncertainties relate to the relative survival benefit from early versus late HSCT, the proportion detected due to

		▪ Threshold analysis to explore the potential economic impact on those with a false-positive TREC test result and the impact of diagnosing otherwise healthy infants with non-SCID TCL (defined as 'disbenefit').	a family history and the disbenefit experienced by non-SCID TCLs and false positive cases detected in screening.
van der Ploeg 2019[197] Netherlands	Univariable and multivariable sensitivity analysis	▪ Varying parameters values including incidence, survival, cost of screening test, sensitivity, repeat tests, cost of diagnosis, cost of treatment and discount rates. ▪ Including productivity losses due to absences from work to expand to societal perspective	▪ From the univariable analysis the incidence of SCID, the percentage of infants requiring flow cytometry with screening in place, cost of the screening test, costs of late treatment, and survival after late treatment had the largest impact on the cost-effectiveness estimates ▪ Including all parameters in a multivariable sensitivity analysis leads to a worst case scenario of 252,997.32/ QALY comparing screening to no screening, while in the best case scenario, screening was cost saving at €232,427.54 with a gain of 28.7 QALY per 100,000 infants ▪ Broadening the healthcare perspective towards a societal perspective did not lead to changes in ICER presented
Palko 2020[191] Finland	One-way sensitivity analysis	▪ Varying key inputs, including incidence, birth rate, incidence of non-SCID TCLs, survival likelihoods, family history of SCID, extra number of flow cytometry required, proportion cases below TREC limit, screening test cost, and retest cost.	▪ Results were most sensitive to the cost of the screening test and the incidence of SCID. However, even at the lowest incidence assessed screening would still be considered reasonable.
SESCS 2020[195] Spain	Deterministic and probabilistic sensitivity analysis (10,000 Monte Carlo simulations) Probabilistic scenario analysis	▪ Varying incidence, test sensitivity, test specificity, utility values, test cost, proportion of cases identified by family history, average length of hospital stay, survival and discount rates ▪ Probabilistic scenario analysis: Variations in the means of the distribution functions of three key parameters (the discount rates, the cost of the screening test and the incidence of SCID),	*Deterministic sensitivity analysis* ▪ Results were sensitive to changes in the cost of the screening test the incidence of SCID, percentage of presumptive positive screening results, proportion diagnosed by family history, survival rates, and the discount rates applied. ▪ Results were further impacted by resource use and costs including a higher number of days in non-critical care with early diagnosis, higher salary costs of laboratory personnel, and a higher cost of HSCT. *Probabilistic sensitivity analysis*

		compared to a base case in which the cost of the screening test is €5, the incidence of SCID is 1:50,000 and the discount applied to costs and benefits is 3%.	▪ Results are similar to those of the base case (when the unit cost of the screening test is 6.37 and the incidence of SCID is 1:50,000) however uncertainty around the estimates increased. ▪ Cost and the incremental effectiveness vary; however, screening was consistently shown to have a higher cost and greater effectiveness than no screening. ▪ Cost-effectiveness acceptability curves (considering incidence, test cost, and discount rates) indicate that results are similar if an incidence of 1:50,000 or 1:60,000 is taken while the impact of the cost of the screening test can impact results considerably.

Key: EVPI – expected value of perfect information, HSCT – hematopoietic stem-cell transplantation, ICER – incremental cost-effectiveness ratio, NR – not reported, QALY – quality-adjusted life-year, SESCS - Servicio de Evaluación del Servicio Canario de la Salud, SCID – severe combined immunodeficiency disease, TCL - T-cell lymphopenia, TREC – T-cell receptor excision circle assay, WTP – willingness to pay.
* Results were adjusted to 2021 Irish Euro using consumer price indices and purchasing power parity estimates.

6.3.3.2 Study based on empirical data

The study from the Netherlands that was based on empirical data from a pilot trial provided ICERs of cost per QALY gained with screening.[196] The key outcomes from the study are summarised in Table 6.8 with the following adjusted ICERs noted for each strategy identified:

- Strategy 1 (TREC ≤ 6 copies/3.2 mm): €42,617 /QALY
- Strategy 2 (TREC ≤ 10 copies/3.2 mm): €45,506/QALY
- Strategy 3 (direct referral if TREC levels ≤ 2 copies/3.2 and cases with TREC-levels > 2 to ≤10 requires a second heel prick after seven days): €42,927/QALY.

Key cost outcomes were presented in terms of yearly costs per 100,000 infants. The results of sensitivity analyses were not provided. All three strategies were at or below the typically used WTP threshold in Ireland of €45,000 per QALY gained.

Table 6.8 Base-case results for study based on empirical data*

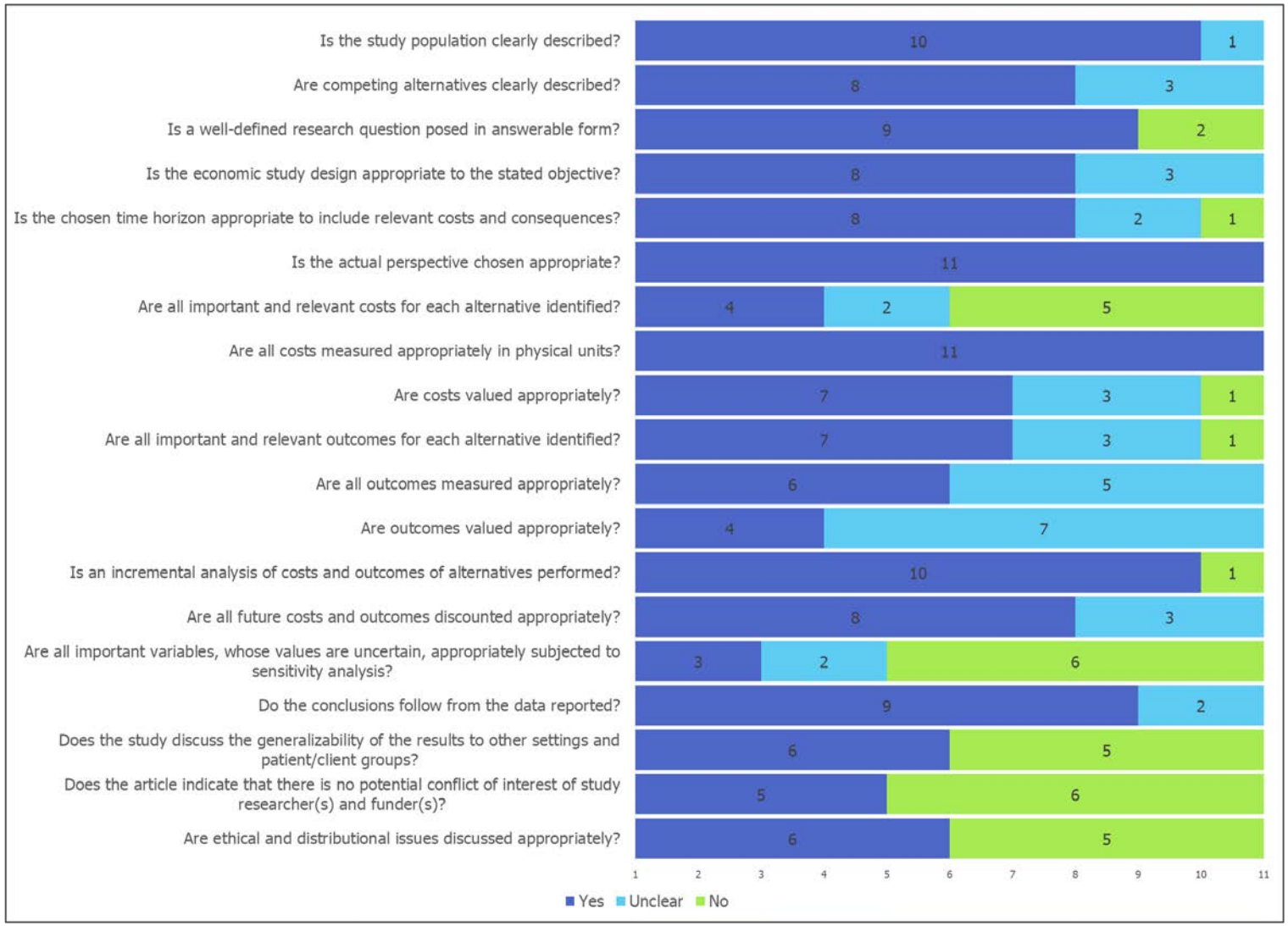
Study Country	Adjusted Key Cost Outcomes*	Adjusted ICER*
van den Akker-van Marle 2021[196] Netherlands	▪ Results presented for a number of screening strategies with yearly costs per 100,000 infants: o Without screening estimated total healthcare costs of €470,955 o Screening with TREC ≤ 6 copies/3.2 mm cut off estimated at €970,596 with 11.7 QALYs gained relative to no screening o Screening with TREC ≤ 10 copies/3.2 mm cut off estimated at €1,003,513 with 11.7 QALYs gained relative to no screening o Direct referral if TREC levels ≤ 2 copies/3.2, and cases with TREC-levels > 2 to ≤10 require a second heel prick after seven days estimated at €973,176 with 11.7 QALYs gained relative to no screening	▪ TREC ≤ 6 copies/3.2 mm: €42,617QALY ▪ TREC ≤ 10 copies/3.2 mm: €45,506/QALY ▪ Direct referral if TREC levels ≤ 2 copies/3.2, and cases with TREC-levels > 2 to ≤10 requires a second heel prick after seven days: €42,927/QALY

Key: ICER – incremental cost-effectiveness ratio, QALY – quality-adjusted life-year, TREC - T cell receptor excision circle assay
* Results were adjusted to 2021 Irish Euro using consumer price indices and purchasing power parity estimates.

6.3.4 Quality appraisal

The methodological quality of the included studies was variable, as illustrated in Figure 6.4 and Appendix 6.4. Studies were considered to be of high (n=2),[101, 195] moderate (n=2),[188, 198] or low (n=7),[190-194, 196, 197] quality based on the information reported. The most common issues related to failure to clearly incorporate relevant costs and outcome data relating to non-SCID TCLs, inadequate descriptions of outcome measurement and valuation sources, insufficient or unclear sensitivity analyses performed, and inadequate discussion or consideration of ethical issues resulting from screening for SCID, such as false positives and non-SCID TCLs detected through screening.

Figure 6.4 Methodological quality assessment of economic evaluations using CHEC-list



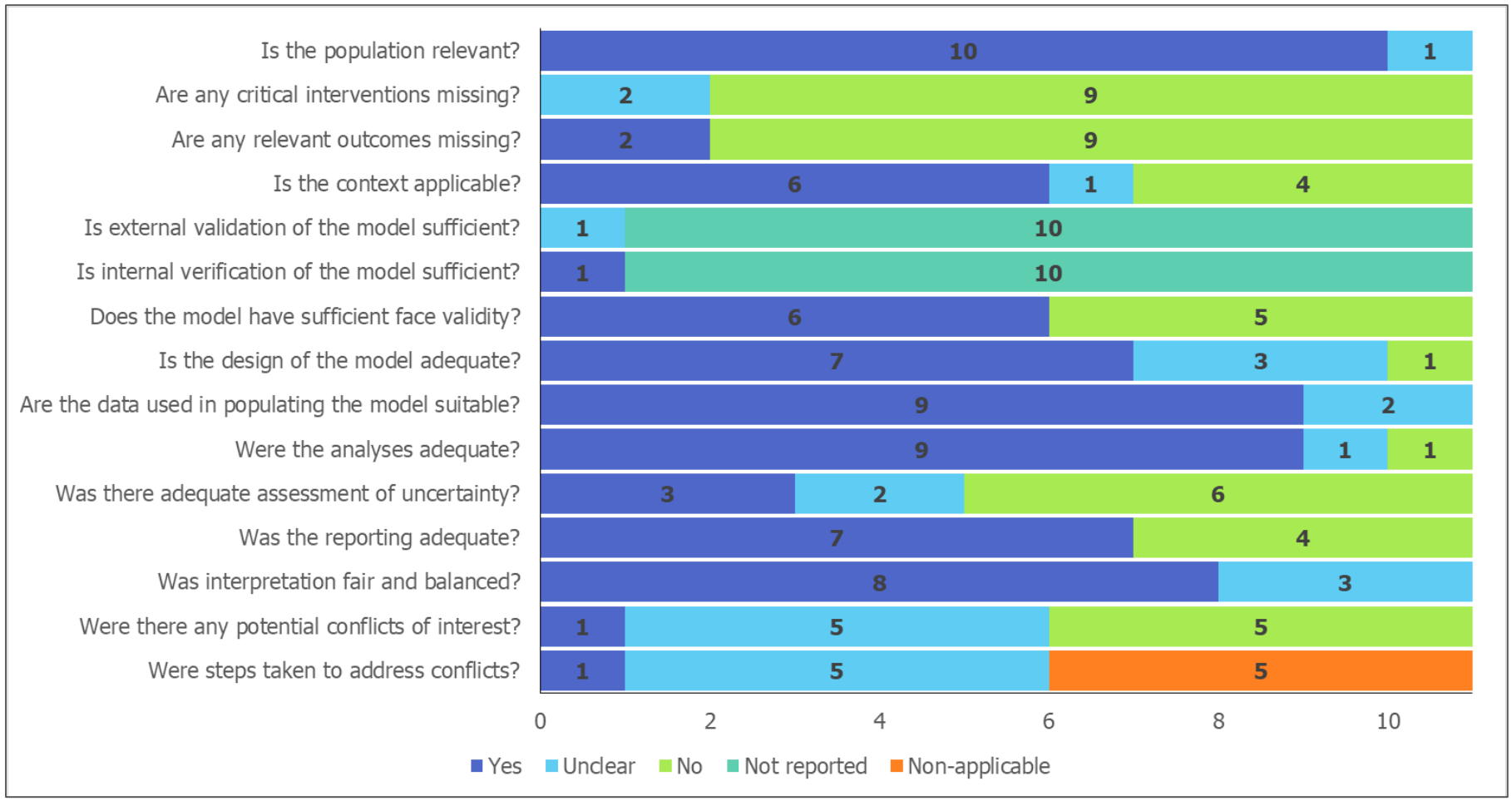
6.3.5 Applicability of the evidence

The results of the assessment of applicability of the included studies is illustrated in Figure 6.5 and Appendix 6.5. As no study was identified from an Irish setting and no study considered a comparison of screening for ADA-SCID, no included study could be considered directly applicable to the Irish context. However, two studies were judged to be largely applicable to the Irish setting in the context of the available data for this rare and heterogeneous disease.[101, 195] Two additional studies were determined to be partially applicable; however, there were overall limitations in the analysis performed.[194, 197] Four studies set in the context of US and Canadian healthcare perspectives were not considered applicable to the Irish context, due to the differences in health systems and associated costs.[188, 190, 192, 193] Two additional studies were not considered applicable due to inadequate reporting and poor documentation which limited interpretation of the methods and results.[191, 196]

The two studies considered to be largely applicable to the Irish setting were performed in the UK and Spain.[101, 195], with the Spanish analysis being an adapted version of the UK model. As expected, given the high incidence of SCID in Ireland as described in chapter three, the incidence of SCID used in these studies was lower than that in Ireland. The context of the analyses was considered appropriate to the Irish setting in terms of healthcare systems and the intervention of interest, with a proportion of cases further detected through family history. The data used to populate the analyses, in terms of test and treatment outcomes, were considered largely in line with that expected from the reviews completed in this report, with both also including estimates of costs associated with the identification of non-SCID TCLs as part of screening. However, as highlighted previously, under the current pathway of care, HSCT for Irish patients with SCID is performed in the UK with contract costs billed at a fixed cost; therefore, estimates relating to cost differences in terms of earlier versus later treatment are challenging to quantify. The methods used to estimate utility data were considered to be appropriate in the context of the challenges associated with these estimates in rare paediatric diseases generally. The choice and structure of the analyses were considered to be appropriate, and both undertook suitable sensitivity analyses to quantify uncertainties in key parameter data.

Again, it should be emphasised that while the evidence presented represents the best available in terms of the introduction of universal TREC-based screening for SCID, no study was identified which included a comparison of screening for SCID with screening for ADA-SCID alone. Therefore, the incremental cost-effectiveness of TREC-based screening for SCID relative to ADA-SCID is unclear.

Figure 6.5 Applicability of economic evaluations to the Irish context



6.4 Discussion

The aim of this chapter was to synthesise the available international evidence on the cost effectiveness of TREC-based newborn screening for SCID compared with no screening or with screening for ADA-SCID alone, and to assess the applicability of the evidence to the Irish context. A total of 11 independent studies were included in the synthesis overall, all of which compared screening for SCID with no universal screening; no comparisons with screening for ADA-SCID alone were identified.[101, 188, 190-198] Ten of the studies (including the two linked publications) were model-based analyses,[101, 188, 190-195, 197, 198] and one study was an adaption of an included model-based study,[197] using empirical data from a pilot study in the Netherlands.[196] Result were converted to 2021 Irish Euro to facilitate comparisons between studies and were interpreted in the context of WTP thresholds typically used in Ireland to inform decision making. The majority of the included studies reported ICERs below the WTP threshold of €45,000 and therefore may be considered potentially cost-effective at this threshold.

It should be emphasised that while the evidence presented represents the best available in terms of the introduction of universal TREC-based screening for SCID, as noted above, no studies were identified that compared screening for SCID to screening for ADA-SCID alone. As of May 2022, universal screening for ADA-SCID has been implemented in Ireland. Notably in Ireland, as outlined in chapter three, there is a higher proportion of patients with ADA-SCID compared with other countries. The current context in Ireland of ADA-SCID screening represents a relatively unique scenario which has implications for the evaluation of the cost effectiveness of screening for SCID. If screening for ADA-SCID had been in place in the studies examined within the present review, the incremental benefits would be expected to be lower as a proportion of the cases would already have been detected through such screening. However, the incremental costs would not be expected to be correspondingly lower. This would be expected to result in higher ICERs (that is, it would be less cost effective) than the estimates observed. In understanding the relevance of this to Ireland, it is also important to note that these expectations are however also dependent on the incidence of SCID and will be influenced by the presence and size of an undiagnosed population (that is, those who may die prior to clinical presentation) which is challenging to reliably estimate.

It is important to note that, overall, there was a large amount of uncertainty in the identified studies in terms of the model inputs and, thus, outcomes. Most studies reported that the models appeared to be sensitive to variations in a number of key variables, including: test specificity, incidence of SCID, test and diagnostic costs, the cost of treatment (especially costs of treatment for late detected SCID cases), and

survival post treatment. These inputs can be difficult to estimate given the rarity in the condition, leading to difficulties in obtaining estimates of the costs associated with various steps of the diagnostic and treatment pathways, as well as differences in outcomes and incidence between populations.[199] Furthermore, the use of QALYs in NBS research has been highlighted as challenging given the requirement for information regarding utility measures in newborns which is notably difficult to obtain and interpret in the context of rare paediatric diseases.[199]

Of note, the two studies from the Netherlands presented in this review offer important comparisons of the potential differences between model-based studies and those based on empirical data.[196, 197] The earlier study was a model-based study of a hypothetical cohort, and the later study was an adaption of the model based on data from a pilot implementation trial for universal SCID screening. There was a large difference in the estimated ICERs between the two studies, whereby the ICER was larger (that is the universal screening was less cost effective) in the study which used empirical evidence from the pilot trial. During the course of the implementation trial, the TREC-cut off values were adjusted to be more sensitive in order to ensure no atypical SCID cases were missed. There was also a post-hoc screening algorithm explored. The comparison of these two studies highlight the uncertainty in results from modelling to reflect real-world scenarios. This difference in the studies may highlight the importance of real-world data in an economic evaluation of screening for SCID; however, as discussed further below, the rarity of the condition limits the feasibility of data collection, resulting in a lack of high-quality, long-term data to inform decision-making.

In the course of the completion of this work, three other literature reviews of economic evaluations for SCID screening were identified. These included a 2020 review from Spain which was included in the same publication as the economic evaluation included in this report,[195] a 2022 report from Canada (Quebec),[77] and a 2022 report from France.[82] Similar studies to those in this current review were identified and included in the three other reviews, however this current review was performed according to principles of a systematic review, and identified a larger number of relevant studies and included more recent literature. Overall, despite the high degree of heterogeneity between the included studies, the reviews reported similar findings in terms of the potential cost effectiveness of introducing TREC-based screening for SCID into a NBS programme compared with no screening.

In addition to the literature reviews identified since completion of this systematic review, an additional relevant primary research study was identified that was published after the search date.[200] This economic evaluation, which was conducted in Australia from a healthcare system perspective, was a CUA exploring the cost effectiveness of universal screening for SCID compared with no screening. The

results of the study were consistent with the results from the other studies included within this review, demonstrating that addition of screening for SCID to an established NBS programme was potentially cost-effective at a WTP threshold of €45,000 (adjusted ICER: €28,264/QALY).

Limitations and feasibility of an Irish specific model

Overall, while no identified study was considered to be directly applicable to the Irish context, two studies, from the UK and Spain, were considered to have sufficient applicability to Ireland to inform decision-making.[101, 195] Both presented ICERs considered to be potentially cost effective at the WTP of €45,000.

Based on the findings of this review, performing a de novo cost-effectiveness analysis within the Irish setting is unlikely to provide additional value. Although Irish epidemiology sources exist for some of the key variables identified, they are associated with numerous limitations due to the rarity of SCID and the relatively small annual birth cohort in Ireland compared with that in countries such as the UK. Similarly, estimates specific to the Irish context for elements such as the impact of early versus late treatment are likely to be difficult to obtain given that HSCT for patients with SCID in Ireland is currently provided in the UK (of note, a HTA of the potential for repatriation of care to inform decision making by the HSE is ongoing at the time of writing). There would also be challenges in estimating the prevalence of non-SCID TCLs and their associated diagnostic and treatment costs over a sufficient time horizon, leading to further uncertainty in any potential model. In the context of the implementation of universal screening for ADA-SCID (May 2022), there are likely to be challenges in obtaining reliable estimates for this comparator given its recent introduction in Ireland and its novelty in the international landscape. Other countries have taken the approach of conducting pilot studies to obtain parameter data to inform cost effectiveness analyses; including a two year pilot in the UK that is ongoing at the time of writing following a recommendation from the UK NSC.[58] However, given the small birth cohort in Ireland, such pilot studies are unlikely to be feasible or useful for gathering reliable estimates. Therefore, it is likely that many of the parameter estimates required to support a cost-effectiveness model aimed at representing the Irish setting would need to be sourced from the studies included in the present review, such as the UK, with no reduction in the uncertainty presented in the current review. Irrespective of the findings of a CEA, a detailed budget impact analysis will be required to inform the affordability of screening for SCID in Ireland given the likely resource and organisational implications.

6.5 Conclusion

Results from the identified economic evaluations indicate that universal screening for SCID may be a cost-effective intervention compared with no screening. Seven studies provided ICERs for cost per QALY gained with screening, with six studies reporting an ICER below the WTP of €45,000 per QALY. However, no studies were identified that compared screening for SCID with screening for ADA-SCID alone (that is, the current standard of care as of May 2022). In understanding the potential relevance of the results of the review, it is important to note that, were screening for ADA-SCID in place, the incremental benefits would be expected to be lower; this is because a proportion of the cases would already have been detected through such screening. However, the incremental costs would not be expected to be correspondingly lower. This would be expected to result in higher ICERs (that is, it would be less cost effective) than the estimates observed.

Despite the limitations identified in the included studies, the findings presented here represent the best available evidence for the cost effectiveness of the introduction of universal SCID screening to a NBS programme. The completion of a de novo cost-effectiveness analysis for Ireland is unlikely to provide additional insight given limitations in data availability. However, a detailed budget impact analysis will be required to assess the affordability and resource implications to inform implementation and planning of such an addition to the Irish NNBSP.

7. Budget impact analysis

Key points

- Cases of severe combined immunodeficiency (SCID) are currently identified by ADA-SCID screening, family history or clinical presentation. A budget impact analysis was undertaken to estimate the incremental budget impact associated with the addition of T-cell receptor excision circles (TREC)-based screening for SCID to the current standard of care.
    - The aim of adding TREC-based screening for SCID to the existing NNBSP is to enable early identification of SCID cases who are currently diagnosed based on clinical presentation. Screening also aims to identify any SCID cases not captured by current practice (that is, there may be a proportion of cases who die prior to clinical presentation or diagnosis).
- The budget impact analysis was undertaken in two parts to reflect costs associated with different parts of the screening programme:
    - verification and implementation of screening (for example, costs associated with laboratory equipment and staffing)
    - diagnosis and treatment (for example, costs associated with hospital admission or outpatient appointments).
- The incremental budget impact associated with **verification and implementation** of TREC-based screening for SCID, in addition to current practice, was estimated at **€3.0 million over a five-year time horizon**. The incremental budget impact was driven largely by the cost of the TREC test kit (consumables), equipment and labour.
    - In one-way sensitivity analysis, the major contributor of uncertainty to the incremental budget impact related to the unit cost per TREC test kit.
    - The results were robust in other investigated scenario analyses. The base case assumed implementation in the current National Newborn Bloodspot Screening Laboratory (NNBSL) in Children's Health Ireland (CHI) Temple Street which would necessitate renovations. If implementation of TREC-based screening were to be deferred until the laboratory at the new National Children's Hospital is operational, first year implementation costs would be lower (approx. €133,000).

- New equipment accounts for approximately 9% of the total incremental budget impact. There may be potential for efficiencies for the HSE if this equipment is also used for other purposes in the future.

- The **diagnosis and treatment** of SCID and non-SCID T-cell lymphopenias (TCLs) as identified through screening, was estimated to result in an incremental budget impact of approximately **€660,000 over a five-year time horizon**.
  - Earlier diagnosis of SCID cases, who present clinically under current practice, was associated with a partial cost-offset owing to a reduction in resource use and treatment costs for these patients.
  - Given the assumptions around a possible increase in post-screening prevalence, the majority of this incremental budget impact was associated with the identification of SCID cases that would not have been diagnosed in the absence of screening (that is, those who may die prior to clinical presentation). These assumptions are associated with substantial uncertainty; when explored in scenario analysis they were noted to be a significant driver of the budget impact.
  - Uncertainty associated with estimates of the numbers of currently undiagnosed non-SCID TCL cases, who might be identified through screening, were also found to have a considerable impact on the incremental budget impact in scenario analysis.
- If a decision were made to implement TREC-based screening for SCID, the outcomes of screening in the Irish context would be dependent on the results of verification of the testing method and establishment of population norms.
- With the exception of the previously undiagnosed population, this analysis considered the cost of management up to the point of HSCT. Currently HSCT for SCID is accessed in the UK through the Treatment Abroad Scheme at a fixed cost, irrespective of the clinical circumstances at the time of referral. Repatriation of HSCT services for this population is subject to an ongoing HTA to inform decision making by the HSE.
- The total incremental budget impact is estimated at €3.66 million over five years. The certainty of the results is limited by the availability of data to consider all relevant clinical and economic consequences. Key uncertainties include the cost of the TREC test kit, the number of abnormal TREC screens, care pathways for non-SCID TCLs, and the incidence of undiagnosed SCID.

7.1 Introduction

The purpose of this analysis is to estimate the resource and financial consequences for the Irish healthcare system associated with the addition of T-cell receptor excision circles (TREC)-based screening for severe combined immunodeficiency (SCID) to the National Newborn Bloodspot Screening Programme (NNBSP).

This analysis sought to include the full clinical pathway from sample collection to treatment. With consideration to the rarity and clinical heterogeneity associated with of SCID and non-SCID T-cell lymphopenias (TCLs), reliable estimation of treatment costs was challenging. With consideration to the limitations in the evidence base, the incremental budget impact was assessed in two parts to reflect costs associated with different parts of the screening programme:

- part 1: verification and implementation of screening (for example, laboratory equipment, consumables, recruitment of staff)
- part 2: diagnosis and treatment (for example, hospital admission, outpatient appointments, immunoglobulin replacement therapy, antibiotics).

7.2 Methods

The budget impact analysis (BIA) was conducted in accordance with the Health Information and Quality Authority (HIQA) guidelines for budget impact analysis and economic evaluation in Ireland,[185, 201] using the Excel 2013 and R Studio (version 3.6.2) software packages.

A list of model assumptions and justifications is presented in Supplementary Appendix 7.1.

7.2.1 Target population

The target population of the assessment is newborn babies for whom parental or caregiver consent has been received to participate in the NNBSP in Ireland. It was estimated that approximately 58,000 newborns annually would be eligible for screening based on the Central Statistics Office (CSO) population projections (see Table 7.1).[100]

The CSO report contains two assumptions on internal migration: the 'Dublin Inflow' and 'Dublin Outflow' scenarios. For the purposes of this analysis, the 'Dublin Outflow' scenario was assumed to more likely reflect the migration pattern among young families; this assumption is in line with the approach taken by the Department of Education in projecting school enrolments from 2021-2036.[202]

The uptake rate of screening was assumed to be 99.9%, consistent with the current uptake rate for newborn screening.[19]

Table 7.1 Projected annual births†

Year	Estimated births (n)
2024	58,392
2025	57,962
2026	57,689
2027	57,455
2028	57,475

† Projected annual births were calculated by the Central Statistics Office and based on the 2016 census.[203] Population projections are available for six different population outcomes resulting from the combination of assumptions regarding fertility, mortality, internal migration and international migration. In the base case analysis, decreasing fertility, high net inward migration and population outflow from Dublin was assumed. Variation in annual births between Dublin outflow and inflow scenarios is typically less than three births per annum during the years considered (2025 to 2028).

7.2.2 Intervention and comparator

A detailed description of the technology is provided in chapter 2. Briefly, as part of the current NNBSP programme, a blood sample is taken from the baby's heel (that is, the 'heel prick test') in the first 72 to 120 hours after birth. The blood sample is processed to detect nine rare, but serious health conditions (chapter 2, section 2.2.1). Screening for ADA-SCID (that is, a subtype of SCID) using tandem mass spectrometry was implemented in May 2022. The parent(s) or legal guardian(s) of infants with an abnormal screening result are contacted and clinical pathways initiated as appropriate to the condition detected.

This assessment considers all potential changes necessary to the current NNBSP associated with the addition of TREC-based newborn screening for SCID with a view to calculating the incremental budget impact associated with this addition. It was assumed that the current practice of detection via family history and ADA-SCID screening would continue, while TREC-based screening for SCID was assumed to detect infants with other subtypes of SCID earlier than would occur based on clinical presentation. Screening also aims to identify any SCID cases not captured by current practice (that is, there may be a proportion of cases who die prior to clinical presentation or diagnosis). The budget impact considers potential costs associated with introduction of TREC-based screening as well as cost offsets that may arise due to early detection of SCID for those cases which would currently present clinically.

7.2.3 Perspective and time horizon

The BIA estimated the incremental cost associated with the addition of TREC-based screening for SCID to the NNBSP over a five-year time horizon.

The analysis adopts the perspective of the Irish publicly-funded health and social care system, namely the Health Service Executive (HSE). Accordingly, only direct medical costs to the HSE were considered. Indirect costs such as productivity losses associated with morbidity and mortality, and out-of-pocket expenses incurred by individuals attending follow-up appointments, where necessary, were excluded from the analysis.

7.2.4 Input parameters

Model input parameters were estimated using a range of methods as appropriate to each input, in line with the published protocol.[180] Specific estimates are described separately below.

Given the rarity of the condition, coupled with the small annual birth cohort size in Ireland, available national data sources are associated with considerable uncertainty. Where estimates were derived from the published international literature, they were corroborated by national data sources, where available, and expert clinical input.

For part one of the BIA, set up and verification of TREC-based screening for SCID was assumed to take nine to 12 months, based on consultation with the NNBSP.[204] Therefore, it was assumed that TREC-based screening for SCID would commence in year two of the budget impact analysis.

Screening test outcomes

As described in chapter 4, section 4.1.1, within the context of a screening programme for SCID, only those with an abnormal TREC-based screening result are referred for flow cytometry to confirm a diagnosis of SCID or other TCLs.

The rate of detection of SCID, non-SCID TCLs, and instances of false positives are dependent on the TREC cut-off and algorithm in use. Therefore, if a decision were made to implement TREC-based screening for SCID, the outcomes of screening in the Irish context would be dependent on the results of the verification of the testing method and establishment of population norms. For the purposes of this assessment, estimates were based on the published literature and expert clinical judgement (chapter 4 and Table 7.2). The influence of uncertainty in testing outcomes on the incremental budget impact was investigated in sensitivity analysis (section 7.2.5).

It was assumed that 0.033% (95% confidence interval (CI): 0.007 to 0.123) of TREC screens would be abnormal and require confirmatory testing with flow cytometry (Table 7.2). This would correspond to approximately 17 abnormal TREC screens (95% CI: 4 to 72) per annum based on a projected population of approximately

58,000, assuming 99.9% uptake. In the base case analysis, the estimate was based on the median value for this parameter from studies included in the systematic review of TREC-based newborn screening (chapter 4, Table 4.4). The uncertainty surrounding this parameter was estimated from the range of plausible values in included studies; this was conducted using the fitdistrplus package (version 1.1-8) in R, assuming a beta distribution.

Table 7.2 Testing outcomes of TREC-based screening for SCID used in the base case analysis†

Parameter	Estimate	95% CI	Distribution	Source
Abnormal TREC screens	0.033%	(0.007 to 0.123)	beta	chapter 4
PPV	47.69%	(16.84 to 90.56)	beta	chapter 4

Key: CI – confidence interval; PPV - positive predictive value; TREC - T-cell receptor excision circles.
† Testing outcomes are based on the median value of studies included in the systematic review of TREC-based newborn screening (chapter 4). Uncertainty associated with testing outcomes was investigated in scenario analysis.

Epidemiological outcomes

The estimated proportion of cases identified by ADA-SCID screening, family history, or clinical presentation was based on historical cases in Ireland (Table 7.3). It was assumed that these proportions would remain similar in the context of TREC-based screening. Those previously diagnosed by clinical presentation (that is, late diagnosis) would be identified by TREC-based screening (that is, it would result in early diagnosis). Additionally, it was assumed that under current practice a proportion of infants die prior to diagnosis of SCID (that is, a previously undiagnosed population) and that such infants would be identified by TREC-based screening.

Estimates of the potentially undiagnosed SCID population were informed by the epidemiology of SCID in Ireland and the international literature as follows. The prevalence of SCID in Ireland is estimated at 1 in 39,760 births (chapter 3). This represents the lower bound for the expected prevalence after the introduction of TREC-based screening for SCID (that is, the post-screening prevalence was assumed to be greater than or equal to the current prevalence). Based on the international literature, the highest estimated prevalence of SCID is 1 in 22,159 births.[108] In the base case analysis, the mid-point of the upper and lower bounds for the plausible range was assumed to represent the post-screening prevalence (that is, 1 in 28,458 births).[108] In absolute numbers, this represents approximately one additional SCID case every second year, in the context of a current detection rate of approximately 1.45 cases of SCID per year. It was assumed that this potential undiagnosed population would comprise non-ADA-SCID cases, as it is considered unlikely that cases of ADA-SCID have not been identified by past or current practices (that is, the

past use of targeted screening for ADA-SCID in at-risk populations, and the current use of highly sensitive ADA-SCID screening in the NNBSP).

Table 7.3 Epidemiology of SCID pre- and post-TREC-based screening for SCID

Parameter	Estimate	Source(s)	Assumptions
Pre-TREC-based screening for SCID†			
Prevalence of SCID	1 in 39,760	chapter 3	NA
Proportion of cases diagnosed by family history	0.11	chapter 3	NA
Proportion of cases diagnosed by ADA-SCID screening	0.52	chapter 3	NA
Proportion of cases diagnosed clinically	0.37	chapter 3	NA
Post-TREC-based screening for SCID‡			
Prevalence of SCID (incorporating cases that previously would have gone undiagnosed)	1 in 28,458	chapter 3; Rechavi 2017[108]	Midpoint of assumed upper and lower bounds
Proportion of cases diagnosed by family history	0.08	chapter 3	Assume no change in the absolute number of cases diagnosed by family history
Proportion of cases diagnosed by ADA-SCID screening	0.37	chapter 3	Assume no change in the absolute number of ADA-SCID cases
Proportion of cases diagnosed earlier by TREC-based screening	0.26	chapter 3	Assume cases previously diagnosed clinically are identified by TREC-based screening
Proportion of cases previously undiagnosed	0.28	chapter 3; Rechavi 2017[108]	Based on international literature

Key: ADA-SCID - Adenosine Deaminase Deficiency Severe Combined Immunodeficiency; NA – not applicable; TREC - T-cell receptor excision circles
† Proportions are based on cases of SCID diagnosed in Ireland between 2005 and 2020.
‡ Based on national clinical data and estimates of the undiagnosed population (these based on the published literature).

Clinical outcomes

Estimates of resource use and treatment requirements were informed by consultation with clinical experts (Table 7.4). Based on the experience of managing cases of SCID in Ireland to date, patients identified by family history (that is, early diagnosis) are typically managed as outpatients. Sixty percent of patients diagnosed early require inpatient admission for diagnostic follow-up (typical length of stay 14 days). To reduce the risk of infection, immunoglobulin replacement therapy (IgRT) is

administered every three weeks until haematopoietic stem cell transplantation (HSCT).

Patients diagnosed by clinical presentation (that is, late diagnosis) are typically admitted at the point of diagnosis until definitive treatment due to the presence of infectious complications (typical length of stay 65 days). Patients presenting clinically typically require higher doses of IgRT (IgRT weekly until HSCT) and treatment for infection(s) at the time of diagnosis.

In the absence of evidence, estimated resource and treatment requirements for non-SCID TCLs are based on expert opinion. It was assumed that patients with non-SCID TCLs would be managed as day cases or outpatients. In the base case analysis, it was assumed that 50% of cases would require a full panel genetic test and 25% would require day case admission for IgRT.

For children with SCID, HSCT is currently accessed in the UK through the Treatment Abroad Scheme. The cost of the procedure is largely fixed, that is, the costs for the procedure do not vary irrespective of the clinical circumstances at the timing of referral for HSCT. Given the current procurement arrangements, it was assumed that TREC-based screening for SCID would not impact HSCT treatment costs for the population that would be identified by clinical practice. That is, potential cost-offsets associated with early diagnosis were limited to pre-HSCT reductions in hospital admissions and treatment). For the SCID population that previously would have gone undiagnosed, additional treatment costs associated with HSCT were included.

Table 7.4 Resource use and treatment requirements†

Parameter	Estimate	Assumptions
SCID - Early diagnosis		
Number of outpatient appointments pre-HSCT	9.00	NA
Percentage requiring genetic testing	100%	Assume subset of genetic panel
Percentage admitted for diagnostic follow-up	60%	NA
LOS for diagnostic follow-up	14 days	NA
Percentage admitted due to infectious complications	0%	Patients diagnosed early may still acquire infections, but can be managed as outpatients
Percentage receiving IgRT	100%	NA
Day case admissions for IgRT	3	Assume one round every 3 weeks from time of diagnosis until definitive treatment (50 days)
SCID - Late diagnosis		
Number of outpatient appointments per HSCT	0	Patients diagnosed clinically are managed as inpatients
Percentage requiring genetic testing	100%	Assume subset of genetic panel
Percentage admitted for diagnostic follow-up	0%	Assumed that diagnostic follow-up is undertaken during inpatient admission for infectious complications
Percentage admitted due to infectious complications	100%	Patients diagnosed clinically are admitted at the point of diagnosis until definitive treatment; IgRT administered weekly until definitive treatment
LOS for infectious complications	65 days	NA
Non-SCID TCLs		
Number of outpatient appointments	4	The estimated requirements for outpatient appointments reflect resource requirements up to the point of treatment
Percentage requiring genetic testing	50%	Full panel genetic test; assumes differential diagnosis established based on syndromic presentation or other factors for 50% of these patients
Percentage admitted for diagnostic follow-up	0%	NA
Percentage admitted due to infectious complications	0%	NA
Percentage receiving IgRT	25%	Expert opinion

Parameter	Estimate	Assumptions
Day case admissions for IgRT	3	Assume same requirements as SCID patients diagnosed early

Key: CHI - Children's Health Ireland, IgRT - Immunoglobulin replacement therapy, NA – not applicable, SCID - severe combined immunodeficiency, TCL - T cell lymphopenia

† Estimated resource use and treatment requirements for cases of SCID were based on national clinical data for cases of SCID managed in Children's Health Ireland (CHI) at Crumlin between 2005 and 2020. In the absence of data, estimates for non-SCID TCLs were based on expert clinical opinion. Due to the limited sample size of cases of SCID in Ireland, estimation of uncertainty was not possible. Based on the available national data, patients follow structured clinical pathways depending on the timing of diagnosis. Variation in these pathways has not been observed in patients managed in CHI at Crumlin to date.

Costs

All costs presented in Tables 7.5 to 7.8 are valued in 2021 Irish Euro. Where appropriate, healthcare costs were adjusted using consumer price indices (CPI) for health and purchasing power parities (PPP) to the last cost year for which complete data are available (2021), in line with national Health Technology Assessment (HTA) guidelines for the conduct of budget impact analysis.[201] Goods and services were inclusive of value added tax (VAT), at the standard or reduced rate, as appropriate, in line with current VAT rates.[205]

For estimation of staff unit costs, salary scales were identified from consolidated salary scales available from the Department of Health in Ireland.[206] Salary costs were based on mid-point of the scale and adjusted for pension, pay related social insurance (PRSI) and overheads (such as office space, lighting and heating), in line with national HTA guidelines.[201]

Implementation and screening costs

Based on consultation with the NNBSP, there is insufficient space to accommodate TREC-based screening for SCID at the existing site of the NNBSL at CHI Temple Street (section 8.3).[204] In the base case analysis it was assumed that reconfiguration of the existing laboratory would be necessary (Table 7.5). The impact of deferred implementation until the move of the NNBSL to the new children's hospital on the St James's Hospital Dublin campus is complete was explored in scenario analysis (see section 7.2.5).

The cost of laboratory equipment and consumables are subject to uncertainty as public contracts whose monetary value exceeds €25,000 require a formal tendering process prior to procurement, in line with EU Directives and national legislation.[207] It was not possible to accurately estimate the leasing cost per test without engaging in a formal tendering process. As a result, for the purposes of this analysis, it was assumed that all laboratory equipment would be bought rather than leased. Based on consultation with the NNBSP, it was estimated that two thermocyclers (also called polymerase chain reaction (PCR) machines) and two DBS punchers would be required (Table 7.5).[204] The annual maintenance cost was estimated to be 10% of the original purchase price and would apply from year two. Equipment and ICT (updates, Specimen Gate software and printers) costs were recorded as upfront investments.

The cost of TREC test kits was estimated based on the published literature (chapter 6). The influence of uncertainty in the test kit costs on the incremental budget impact was investigated in sensitivity analysis (section 7.2.5). The overall cost of TREC-based screening for SCID took account of the uptake rate (99.9%) and repeat

testing (1.6%) of the NNBSP generally.[204] No modifications to the existing NBS screening card would be necessary.

Following an abnormal TREC screen (estimated 0.03% of all TREC screens, Table 7.2), the newborn and their parent(s)/guardian(s) would be requested to attend the relevant maternity hospital to meet with the local paediatric team for clinical evaluation and initiation of further care pathways, as appropriate, costed as one paediatric outpatient appointment.[208] The total cost of confirmatory testing using flow cytometry comprised an outpatient appointment, sample transport and sample analysis using flow cytometry (Table 7.3). The plausible range of referrals for flow cytometry (95% CI: 0.007 to 0.123%, or four to 72 cases annually, Table 7.2) estimated for the purposes of this analysis are within the available capacity of the Immunology Laboratory at St James's Hospital. Thus, it was assumed that additional recruitment for flow cytometry would not be necessary. In the base case analysis, for non-SCID TCLs and false positive results, it was assumed that confirmatory testing with flow cytometry following an abnormal TREC result would be in addition to existing demand for this service. With consideration to the potential for an undiagnosed population (Table 7.3), it was estimated that 28% of referrals for flow cytometry for SCID would be in addition to current practice (that is, SCID cases diagnosed by ADA-SCID screening, family history or clinical presentation that would have been referred for flow cytometry in the absence of TREC-based screening). Uncertainty regarding the incremental demand for flow cytometry services was investigated in scenario analysis (section 7.2.5).

Based on consultation with the NNBSP, it was assumed that two whole time equivalent (WTE) medical scientists would be recruited for one year to carry out assay verification (that is, establishment of test methodology and population norms).[204] Once assay verification is complete, recruitment of two medical scientists would be necessary to conduct TREC-based screening for SCID at the population level. The unit costs and WTE for the recruitment of additional staff are presented in Table 7.6. All medical scientists would require training on the new method and instrumentation. Based on the experience of the NNBSP, it was assumed that the manufacturer providing test kits and laboratory equipment would deliver initial formal onsite training of recruited medical scientists, and that this should be included in any tender or lease agreement.[204] Training of existing staff was estimated to take 4.5 days.[204] Labour requirements fulfilled by existing staff already employed by the HSE were estimated as opportunity costs (Table 7.7).

At a programme level, it was assumed that no additional staff would be required, provided the current requirements submitted as per the current HSE National Service Plan are met.[204] No additional training of sample takers (that is, nurses, midwives or public health nurses) would be required as there would be no change to the

current practice of taking four bloodspot samples.[204] It was assumed that a voluntary information session advising public health nurses and midwives on changes to the NNBSP would be delivered as part of continuous professional development (CPD) training and would therefore not incur an additional cost.[204]

Diagnosis and treatment costs

Where possible, resource use was estimated using national data sources. Where no clear precedent has been set, resource use was estimated using international data, supplemented by the expert opinion of the EAG. In Ireland, the cost of inpatient care is recorded in the Hospital Inpatient Enquiry (HIPE) system according to Diagnosis-related Groups (DRG).[209] DRGs are designed to group cases which are clinically similar.[209] DRG codes to which children with SCID or other immune system disorders are typically assigned were used to estimate the cost of inpatient care for SCID and non-SCID TCLs. Where average length of stay exceeded the upper boundary, costs were adjusted in line with guidance from the healthcare pricing office (HPO).[209] A weighted average cost for all relevant DRG codes was calculated based on case numbers. Estimates of cost and activity were based on the 2022 Activity Based Funding Admitted Patient Price List.[209]

Diagnosis of SCID prior to symptomatic presentation has been consistently associated with improved patient outcomes (chapter 5) and thus an anticipated reduction in treatment costs due to reduced infection rates and subsequent hospital admissions. Based on the available national clinical data, treatment costs were assumed to be higher for patients diagnosed following symptomatic presentation as more intensive treatment is likely required to stabilise patients presenting clinically (Table 7.4). Potential cost offsets, namely, the reduction in healthcare resource use associated with earlier identification of SCID, were limited to pre-HSCT reductions in hospital admissions and treatment costs. Potential cost offsets associated with HSCT (that is, potential for lower HSCT costs due to less complicated care associated with earlier diagnosis) were excluded as, at present, all care relating to HSCT is provided in the UK at a largely fixed cost as part of the Treatment Abroad Scheme (TAS), irrespective of the clinical circumstances at the time of referral. However, the cost of HSCT was included for potential cases of SCID that would not otherwise be identified by current practice (that is, previously undiagnosed cases who may have died prior to clinical identification).

Following a diagnosis of SCID, is was assumed that infants would receive bridging therapies until they undergo a haematopoietic stem cell transplantation (HSCT); these would comprise IgRT, enzyme replacement therapy (for patients with ADA-SCID) and prophylactic or therapeutic treatment with antibiotics, in line with EBMT and ESID treatment guidelines described in chapter 2.[40, 43] Administration of IgRT

requires day case admission. It was assumed that all care costs related to the admission are included in the estimated DRG-based cost.

Follow-up care for non-SCID TCLs was also considered (that is, genetic testing, outpatient appointments and treatment with IgRT). However, given the uncertainty regarding treatment pathways for non-SCID TCLS, it was not feasible to include specific treatment costs.

Table 7.5 Unit costs of setting up and delivering TREC-based screening for SCID

Parameter	Units	Unit cost	Uncertainty	Distribution	Source(s)	Assumptions
Set-up						
Laboratory modification	NA	€80,000	€64,803 to 96,773	gamma	NNBSP[204]	Assuming immediate implementation
Thermocycler	2	€87,500	€75,000 to €100,000	gamma	NNBSP[204]	Capital investment
DBS puncher	2	€17,500	€15,000 to €20,000	gamma	NNBSP[204]	Capital investment
Printer	2	€2,500	€2,000 to €3,000	gamma	NNBSP[204]	NA
Test kits for verification	5	€7,000	€5,670 to €8,468	gamma	NNBSP[204]	NA
ICT updates	NA	€40,000	€32,402 to €48,387	gamma	NNBSP[204]	NA
Specimen Gate Laboratory software	NA	€20,000	€16,201 to €24,193	gamma	NNBSP[204]	NA
Screening						
SCID screening test†	~58,000 per annum	€5.18	€3.12 to €6.37	gamma	Systematic review of cost-effectiveness (chapter 6); Expert opinion[204]	Includes uptake of NNBSP (99.9%) and repeat DBS samples requested by NNBSL (1.6%)
Quality control for TREC	NA	€0	NA	gamma	NNBSP[204]	Provided by manufacturer
Flow cytometry						
Outpatient appointment following abnormal TREC result	~17 (95% CI: 4 to 72) ‡	€178	€122 to €182	gamma	HSE[210]	NA
Sample transport	~17 (95% CI: 4 to 72)‡§	€248	€201 to €300	gamma	Expert opinion[211]	Emergency samples are transported by taxi
Flow cytometry	~17 (95% CI: 4 to 72) ‡	€222	€180 to €269	gamma	NNBSP[204]	Carried out by existing staff resources
Programme costs						

Parameter	Units	Unit cost	Uncertainty	Distribution	Source(s)	Assumptions
Updating information leaflets (English)	NA	€2,500	€2,025 to €3,024	gamma	NNBSP[204]	Assumed to be a once-off cost
Updating information leaflets (alternative languages)	NA	€1,000	€810 to €1,210	gamma	NNBSP[204]	Assumed to be a once-off cost
Updating eLearning module	NA	€2,500	€2,025 to €3,024	gamma	NNBSP[204]	Assumed to be a once-off cost
Education session for DBS samplers	NA	€0	NA	gamma	NNBSP[204]	Assumed part pf CPD

Key: CPD – continuous professional development, DBS – dried blood spot, ICT – information and communications technology; NA – not applicable, NNBSP – National Newborn Bloodspot Screening Programme, TREC- T-cell receptor excision circles

† The estimated cost of TREC-based screening for SCID in this analysis was considered to be exclusive of equipment and labour costs.

‡ Requirements for confirmatory testing with flow cytometry will be dependent on the proportion of abnormal TREC screens. The proportion of abnormal TREC screens in the Irish context would be dependent on the cut-off used to identify an abnormal result, which would be established during assay verification. For the purposes of this assessment, the proportion of abnormal TREC screens was estimated from the published literature (chapter 4).

§ The cost of taxi transport was estimated based on the distance from each maternity hospital (n = 19) to St James's Hospital, with consideration to population geographic distribution.

Table 7.6 Unit costs for recruitment of additional staff†

Description	Estimated WTE	Unit cost (per annum)	Source(s)
Laboratory modifications			
Project manager	0.5	€117,118	HSE salary scales[206]
Verification			
Basic grade medical scientist	1	€65,043	HSE salary scales[206]
Senior medical scientist‡	1	€82,644	HSE salary scales[206]
Implementation			
Basic grade medical scientist	2	€65,043	HSE salary scales[206]

Key: HSE – health Service Executive, WTE – whole time equivalent
† Salaries are based on mid-point of scale adjusted for pension, pay related social insurance (PRSI) and overheads (such as office space, heating and lighting) as per National HTA guidelines.
‡ Based on mean salary scales for senior medical scientist, with and without designated NFQ Level 9 qualification.

Table 7.7 Unit costs for estimation of staff opportunity costs †

Description	Time (days)	Unit cost (per day)	Source(s)
Training of existing laboratory staff			
Basic medical scientist	4.5 days X 5 WTEs	€292	HSE salary scales[206]
Senior medical scientist‡	4.5 days X 3 WTEs	€374	HSE salary scales[206]
Chief medical scientist	4.5 days X 1 WTEs	€467	HSE salary scales[206]

Key: HSE – health Service Executive, WTE – whole time equivalent
† Salaries are based on mid-point of scale adjusted for pension, pay related social insurance (PRSI) and overheads (such as office space, heating and lighting) as per National HTA guidelines.
‡ Based on mean salary scales for senior medical scientist, with and without designated NFQ Level 9 qualification.

Table 7.8 Unit costs associated with treatment of SCID and non-SCID TCLs

Description	Unit(s) (per patient)	Unit cost	Source(s)
SCID (all subtypes)			
HSCT	1	€291,025	Treatment Abroad Scheme
ADA-SCID			
Enzyme replacement therapy	1 unit per week †	€65,627	Bessey 2019[101]
Early diagnosis of SCID			
Day case admission for IgRT	3 rounds‡	€1,203	ABF 2022 Admitted Patient Price List[209]
Outpatient appointments	6	€178	HSE[210]
Inpatient care for diagnostic follow-up	1 admission (14 days) for 60% of patients	€7,330	ABF 2022 Admitted Patient Price List[209]
Inpatient care for infectious complications	0	€7,330	ABF 2022 Admitted Patient Price List[209]
Late diagnosis of SCID (clinical presentation)			
Outpatient appointments	0	€178	HSE[210]
Inpatient care	1 admission (65 days)	€53,021	ABF 2022 Admitted Patient Price List[209]
Non-SCID TCLs			
Day case admission for IgRT	3 rounds	€1,203	ABF 2022 Admitted Patient Price List[209]
Outpatient appointments	4	€178	HSE[210]
Inpatient care	0	€6,037§	ABF 2022 Admitted Patient Price List[209]

Key: ABF – activity based funding, HSCT - haematopoietic stem cell transplantation, HSE – Health Service Executive, SCID - severe combined immunodeficiency, TCL - T cell lymphopenia

† Assume early diagnosis of ADA-SCID requiring 11 weeks of ERT.[101]

‡ Based on consultation with clinical experts, patients diagnosed by family history or screening (that is, early) typically require one round of IgRT every three weeks until the point of definitive treatment. Patients diagnosed based on clinical presentation (that is, late) typically require one round per week until the point of definitive treatment. The interval between diagnosis and definitive treatment was estimated to be approximately 50 days for both early and late diagnosis.

§ Based on DRG codes associated with immune disorders reported in the 2022 ABF report.[209] Inlier price assumed.

7.2.5 Sensitivity and scenario analysis

One-way sensitivity analysis

Where upper and lower bounds for cost estimates were available based on the input of the Expert Advisory Group (EAG), these bounds were used to investigate uncertainty surrounding the mean value. Where no plausible estimates of uncertainty were available, uncertainty in cost parameters was represented by 20% variation in the mean value.

Of note, not all parameters were varied in the one-way sensitivity analysis (OWSA). Only parameters for which there were plausible estimates of uncertainty were included in the OWSA. It was not considered appropriate to assign arbitrary confidence intervals to these parameters. It was assumed that setting salary costs at the mid-point of the scale sufficiently accounted for uncertainty.

For part I of the BIA, OWSA was conducted by fixing each parameter with a statistical distribution assigned in turn at its upper and lower bounds, while all other parameters were held at the mean. The impact of extreme variation in single input parameters on the model output was presented on a tornado plot.

Feedback from clinical experts highlighted that cases of SCID typically follow an established clinical pathway depending on the timing of diagnosis (that is, early or late). Based on the available clinical data, variation in standard practice has not been observed among cases identified to date. For part II of the BIA, due to the absence of uncertainty estimates for clinical parameters (that is, resource use and treatment), OWSA was not feasible. Uncertainty was explored in scenario analyses, outlined in the following section.

Scenario analyses

Scenario analyses were conducted to assess uncertainty in the model. In each scenario, model assumptions were changed, or a base case parameter was replaced with an alternative estimate (Table 7.9). The following outlines the rationale and approach taken for scenarios relating to the number of referrals for flow cytometry and the potential deferral of implementation until completion of the new children's hospital.

Varying the number of referrals for flow cytometry

Precise estimation of the additional demand for confirmatory flow cytometry testing is challenging given the dependence of testing outcomes on the testing methodology and cut-offs set.

In the base case analysis, it was assumed that referrals for flow cytometry with a false positive screening test result would be in addition to existing demand for this service.

It is likely that some non-SCID TCLs would be diagnosed through current practice. Thus, the incremental cost associated with confirmatory testing for non-SCID TCLs is uncertain. In the base case analysis it was assumed that 100% of referrals for flow cytometry among non-SCID TCLs would be in addition to existing demand for this service. To address uncertainty regarding the number of additional referrals for flow cytometry testing among newborns with non-SCID TCLs, the proportion of non-SCID TCLs that would not have been referred for flow cytometry analysis with current practice was varied while all other inputs were fixed at the deterministic value.

Deferring implementation until the national children's hospital is operational

As noted in section 7.2.4, there is insufficient space at the existing site of the NNBSL at CHI Temple Street to accommodate TREC-based testing for SCID. In the base case analysis, it was assumed that modification of the existing laboratory would be required. In a scenario analysis, the costs associated with a decision to defer any implementation of TREC-based screening for SCID until the new children's hospital is operational were investigated.

Table 7.9 Input parameters used in scenario analysis

Scenario	Parameter	Estimate	Source(s)
Part I			
The TREC test is set to the minimum based on the international literature	Cost of TREC-based screening test	€3.12 per test	chapter 6
The TREC test is set to the maximum based on the international literature	Cost of TREC-based screening test	€6.37 per test	chapter 6
75% of flow cytometry referrals for non-SCID TCLs are additional	Percentage of additional flow cytometry referrals for non-SCID TCLs	75%	Assumption
50% of flow cytometry referrals for non-SCID TCLs are additional	Percentage of additional flow cytometry referrals for non-SCID TCLs	50%	Assumption
Part II			
There is no undiagnosed SCID population (pre- and post-TREC-base screening prevalence are the same)	Prevalence of diagnosed SCID after introduction of TREC-based screening	0.00 per 57,645 annual births	chapter 3
The prevalence of diagnosed SCID after introduction of TREC-based screening is equal to the maximum reported in the international literature	Prevalence of diagnosed SCID after introduction of TREC-based screening	2.60 per 57,645 annual births	chapter 3
33% of non-SCID TCLs require hospitalisation	Percentage of non-SCID TCLs requiring inpatient admission	33%	Assumption
100% of non-SCID TCLs require genetic testing	Percentage of non-SCID TCLs requiring full panel genetic testing	100%	Assumption
Part I and II			
Decrease the number of abnormal TREC screens to the minimum reported in the international literature	Percentage of abnormal TREC screens	0.013% of 57,645 annual births	chapter 4
Increase the number of abnormal TREC screens to the minimum reported in the international literature	Percentage of abnormal TREC screens	0.136% of 57,645 annual births	chapter 4

Key: SCID - Severe Combined Immunodeficiency; TCL – T-cell lymphopenia; TREC - T-cell receptor excision circles.

7.2.6 Quality assurance

The BIA was developed in accordance with national HTA guidelines,[201] and quality assured in accordance with the HTA quality assurance framework.

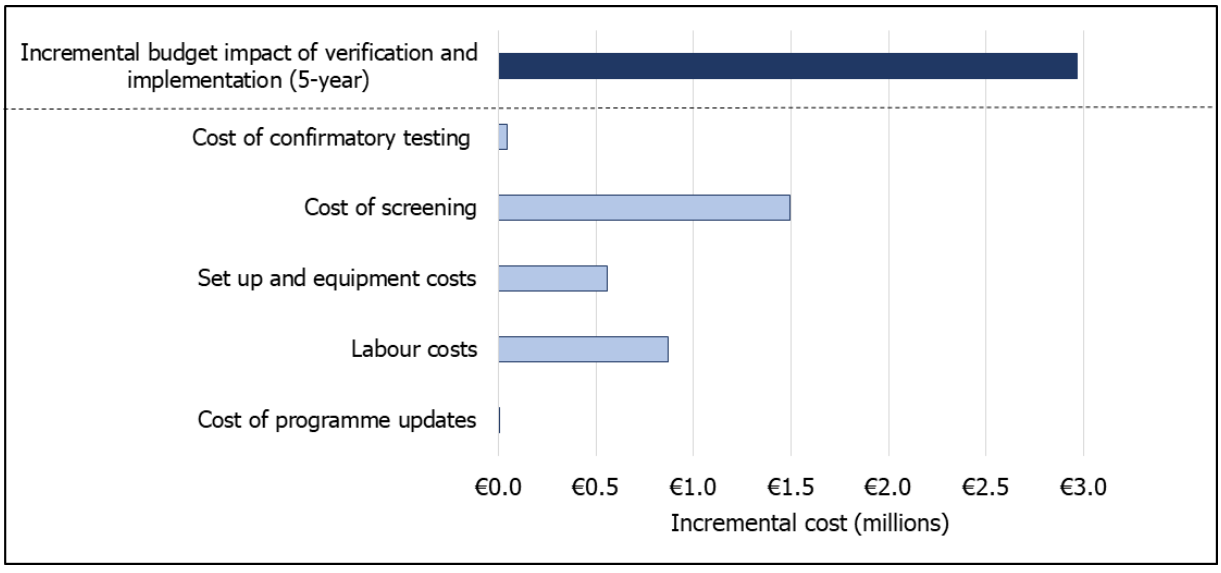
All model inputs and outputs were reviewed by a second member of the evaluation team. Input parameters and assumptions underpinning this BIA were reviewed and endorsed by the EAG.

7.3 Results

7.3.1 Part I: Verification and implementation of TREC-based screening for SCID

Over a five-year time horizon the incremental budget impact for part I was estimated at €3.0 million. The majority of expenditure over a five-year time horizon was associated with the cost of TREC tests (exclusive of equipment and labour) and setting up the laboratory for TREC-based screening (for example, equipment and labour costs) (Figure 7.1). In the base case analysis, given the low expected rate of abnormal TREC screens (Table 7.2), confirmatory testing following an abnormal TREC result comprised a small proportion of the total five-year budget impact.

Figure 7.1 Itemised five-year incremental budget impact of part I (verification and implementation of screening)†



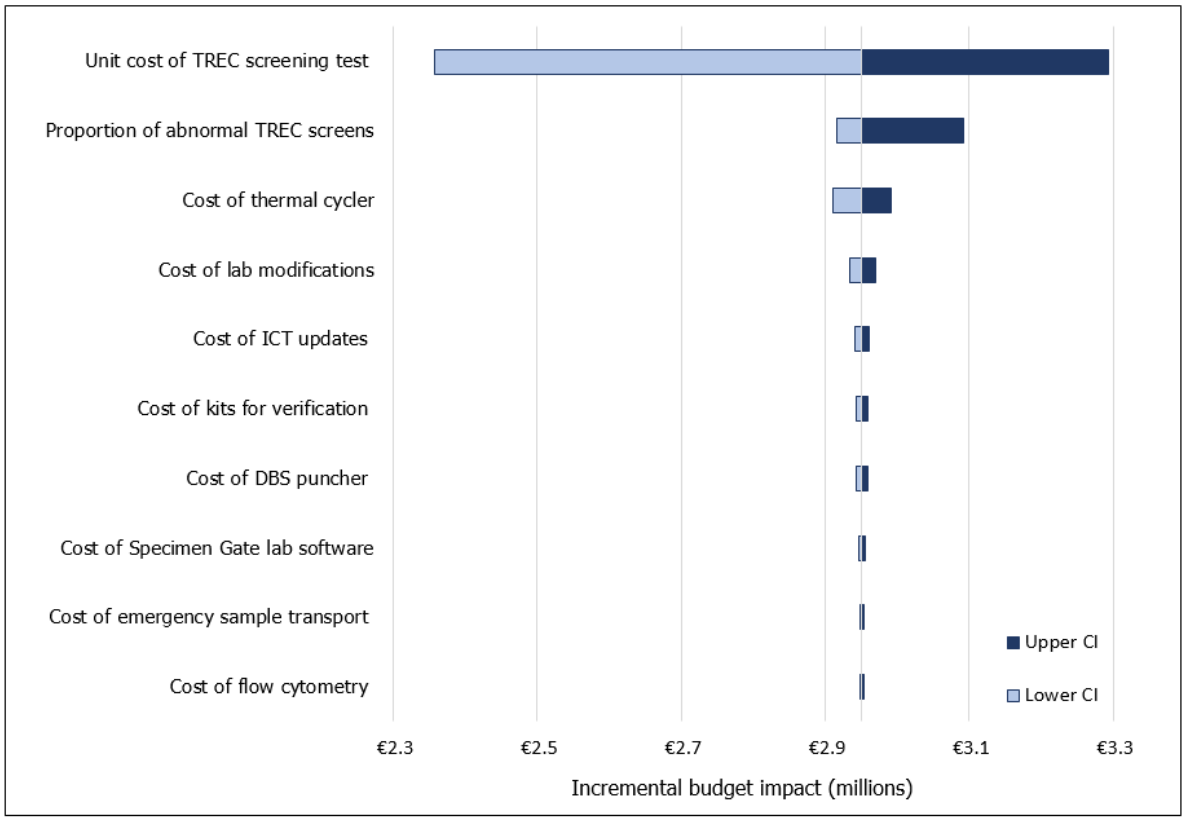
† Set up and equipment costs include the cost of laboratory modification.

Part I: One-way sensitivity analysis

In the OWSA, input parameters were varied and ranked in order of increasing influence on the incremental budget impact. The result is presented as a tornado plot which provides a visual representation of the sensitivity of the model to the uncertainty associated with individual parameters (Figure 7.2). Although all parameters with probability distributions assigned were varied in the analysis, only the ten most influential parameters are presented.

Uncertainty relating to the unit cost of screening was found to contribute most to uncertainty in the incremental budget impact analysis (95% CI: €2.4 to €3.3 million). Other influential parameters included inputs related to the initial set-up of TREC-based screening (for example, the cost of thermal cyclers and ICT updates) and the proportion of abnormal TREC screens requiring further investigation. For the purposes of this analysis, it was assumed that the results of 0.03% of TREC screens would be abnormal and require flow cytometry analysis. In OWSA, varying this parameter between the extremes of the plausible range, based on estimates from the published literature (0.007% to 0.123%), was associated with 6% variation in the incremental budget impact over a five year time horizon (95% CI: €2.9 to €3.1 million). This was attributable to changes in requirements for flow cytometry analysis following an abnormal TREC screen.

Figure 7.2 Tornado plot of one-way sensitivity analysis for the five-year budget impact analysis of part I†



Key: CI - confidence interval, DBS – dried blood spot, ICT - information and communications technology, TREC - T-cell receptor excision circles

† Only costs with plausible estimates of uncertainty were varied in the OWSA. Estimated labour costs were not varied.

Part I: Scenario analysis

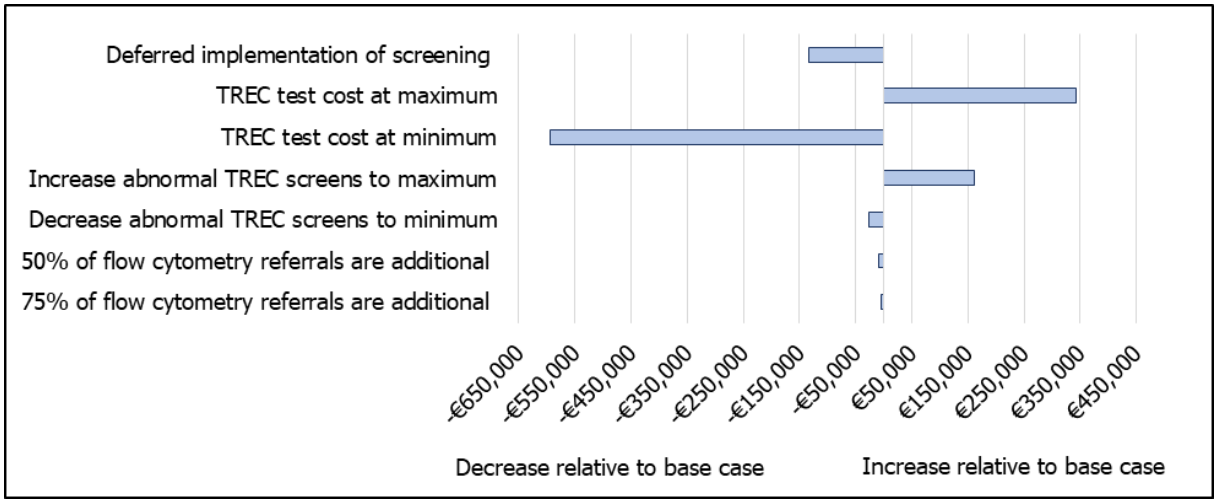
During OWSA, uncertainty associated with the cost of the TREC test kits (consumables) was identified as a key driver in the model. In scenario analysis, setting the unit cost of TREC test kits to €3.12 (that is, the minimum expected cost based on the published literature) was associated with an incremental budget impact of €2.36 million or a 21% reduction in the incremental budget impact relative to the base case analysis (Figure 7.3). Setting the unit cost to €6.37 (that is, the maximum expected cost based on the published literature) was associated with an incremental budget impact of €3.3 million or an 11% increase in the incremental budget impact when compared with the base case analysis.

Assuming that a proportion of non-SCID TCLs are currently being identified and referred for flow cytometry analysis was associated with a small reduction in the incremental five-year budget impact (<€10,000).

Varying the number of abnormal TREC screens to the minimum and maximum bounds of the plausible range of values reported in the international literature did not have a considerable impact on the incremental budget impact. An increase in the percentage of abnormal TREC screens from 0.03% (that is, base case value) to 0.14% (that is, maximum estimated value) would be associated with additional spending of approximately €160,000 in the five-year budget impact related to requirements for onward referral for flow cytometry analysis.

In the base case analysis it was assumed that TREC-based screening would be introduced at the existing site of the NNBSL at CHI Temple Street, requiring reconfiguration of the laboratory (section 8.3). If a decision were made to defer any implementation until the laboratory at the National Children's Hospital on the St James's Hospital Campus is operational, the incremental budget impact would be approximately €133,000 lower during the first year of implementation as the costs associated with reconfiguration of the existing laboratory and oversight of same by a project manager would not be necessary.

Figure 7.3 Results of scenario analysis over a five-year time horizon for part I



Key: TREC - T-cell receptor excision circles
Notes: Alternative estimates for key input parameters were used in scenario analysis. Results are presented as the change in the incremental budget impact for part I relative to the base case estimate (that is, €2,950,937). Maximum and minimum estimates are based on data from the published literature.

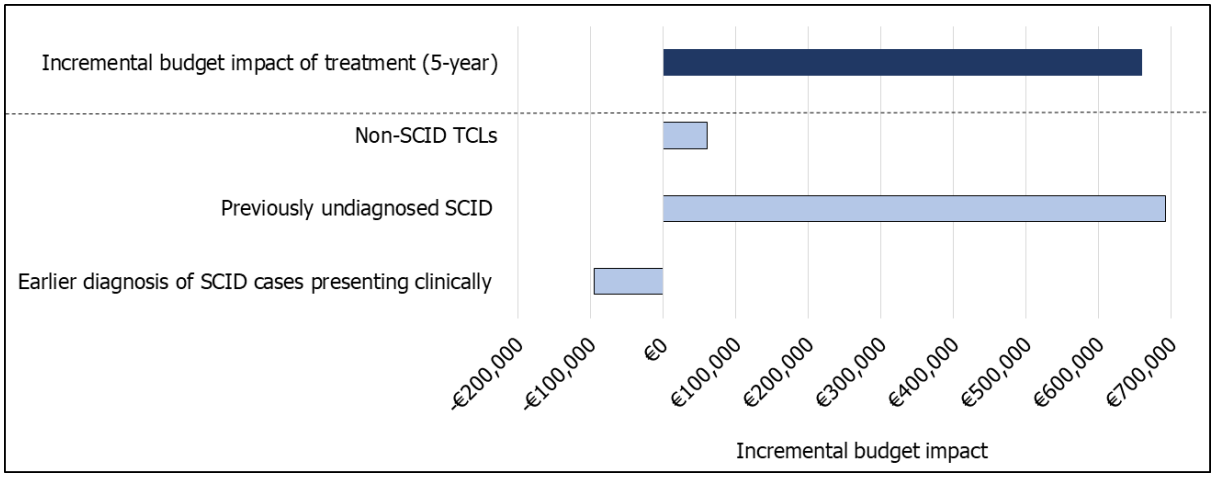
7.3.1 Part 2: Diagnosis and treatment of SCID and non-SCID TCLs

The estimated five-year incremental budget impact associated with the treatment of SCID and non-SCID TCLs identified by TREC-based screening for SCID was €659,816 (Figure 7.4). Earlier diagnosis of SCID cases who would present clinically under current practice was associated with a partial cost offset owing to a reduction in pre-

HSCT resource use and medication costs. A large proportion of the incremental budget impact was associated with the identification of additional SCID cases that would not be identified by current practice, estimated in the base case as one case every two years, resulting in an additional cost of €692,897 (Figure 7.4). In the base case analysis, non-SCID TCLs contributed to a small proportion of the incremental budget impact as it was assumed that non-SCID TCLs would not require inpatient admission.

In the absence of evidence, estimates of the undiagnosed SCID and non-SCID TCL populations are subject to considerable uncertainty and were investigated in scenario analysis.

Figure 7.4 Five-year incremental budget impact of part II by subgroup



Key: SCID - severe combined immunodeficiency, TCL - T cell lymphopenia

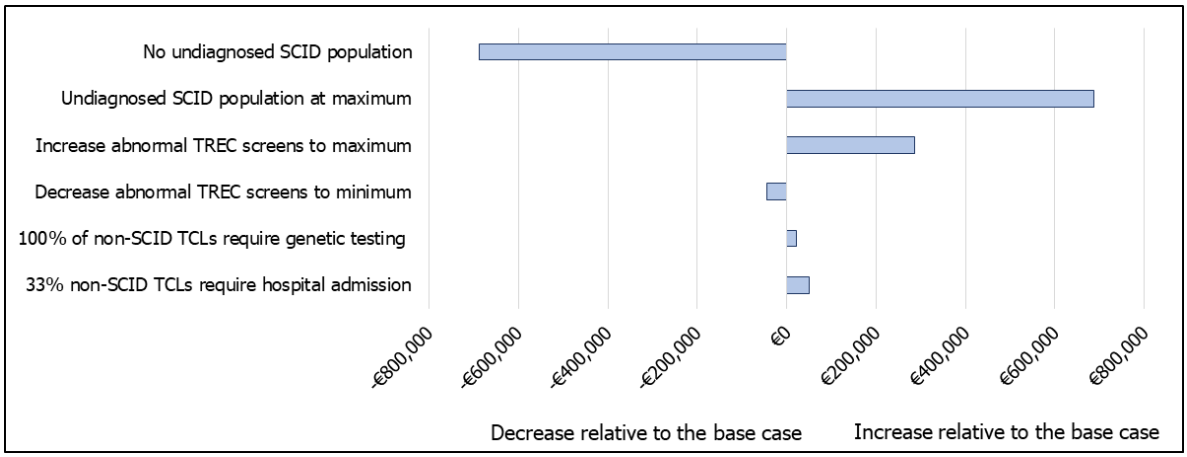
Part II: Scenario analysis

Estimates of the undiagnosed SCID population are subject to considerable uncertainty. Based on epidemiology of diagnosed SCID cases in Ireland from 2005 to 2020 (chapter 3), it is estimated that, on average, approximately 1.5 cases per year are identified with current practice. In the base case analysis, it was assumed that approximately two additional cases would be identified over the five-year time horizon of the BIA following the introduction of TREC-based screening for SCID (that is, the post-screening prevalence would increase). To test this assumption, an analysis was conducted of a scenario of no change in prevalence following the introduction of screening (no additional cases identified). Under these circumstances, the introduction of TREC-based screening would result in cost savings of €27,415 over five years relative to current practice. The cost saving would arise as those usually identified by clinical presentation would be identified at an earlier point on the basis of screening resulting in lower treatment costs for these patients. In a

second scenario analysis, based on the maximum reported prevalence in the international literature (Table 7.9), it was assumed that a further two additional cases would be identified over the five-year BIA. This was associated with additional spending of approximately €687,231 over five years, relative to the base case, largely attributable to the cost associated with HSCT (Figure 7.5).

For this analysis, it was assumed that an increase in the proportion of abnormal TREC screens would result in a relative increase in the number of non-SCID TCLs identified, while the number of SCID cases was assumed to be set at the mean value. Increasing the number of abnormal TREC screens to the estimated maximum value was associated with an increase in the incremental budget impact of €286,510 relative to the base case analysis associated with the management of non-SCID TCLs (Figure 7.5). In the base case analysis, it was assumed that non-SCID TCLs would not require inpatient admission. In scenario analysis, assuming 33% of non-SCID TCLs would require hospitalisation (n = 1 to 2 cases per year) resulted in an increase of €50,021 in the incremental budget impact over the five-year time horizon.

Figure 7.5 Results of scenario analysis relative to the base case over a five-year time horizon for part II



Key: SCID - severe combined immunodeficiency, TCL - T cell lymphopenia, TREC - T-cell receptor excision circles
Notes: Alternative estimates for key input parameters were used in scenario analysis. Results are presented as the change in the incremental budget impact for part II relative to the base case estimate (that is, €659,816). Maximum and minimum estimates are based on data from the published literature.

7.4 Discussion

This budget impact analysis investigated the incremental cost associated with the addition of TREC-based screening for SCID to the NNBSP. Based on consultation with key stakeholders, aspects associated with implementation would include:

- verification and implementation of TREC-based screening (for example, equipment, consumables and labour costs)
- management of SCID and non-SCID TCLs identified.

Verification and implementation

The overall incremental budget impact associated specifically with verification and implementation was estimated at €3.0 million over a five-year time horizon. The incremental budget impact for this aspect was driven largely by the cost of consumables, labour and equipment associated with TREC-based screening. Updating educational resources and confirmatory testing represent a small proportion of the overall incremental budget impact. In OWSA, the cost of the TREC test kits (consumables) was identified as a key driver of uncertainty in the model. For the purposes of this assessment, the unit cost of the TREC assay was based on evidence retrieved in the systematic review of cost-effectiveness (chapter 6). If a decision were to be made to introduce TREC-based screening for SCID, the unit cost of the TREC assay would be dependent on the outcome of a formal tendering process. The incremental budget impact may be substantially reduced if a lower unit cost than assumed in the base case analysis can be agreed. Nevertheless, the unit cost per TREC test assumed for the purpose of this analysis is consistent with the published literature and represents the best available evidence in absence of the outcome of a formal tendering process.

A number of additional assumptions were also tested in sensitivity or scenario analyses for the costs associated with verification and implementation. Of note, in the base case it was assumed that 0.03% of TREC screens would require referral for flow cytometry. In practice, testing outcomes would be dependent on context-specific testing protocols developed during assay verification. Given the uncertainty associated with testing outcomes prior to assay verification, the effect of varying the number of additional referrals for flow cytometry on the overall incremental budget impact was investigated in scenario analysis and OWSA. In OWSA, varying the proportion of abnormal TRECs between the extremes of the plausible range (4 to 72 abnormal TREC screens) was associated with a 6% difference relative to the base case incremental budget impact. Such a change may not represent a substantial affordability issue from a testing perspective, under the assumption that there is

sufficient capacity within existing flow cytometry services to carry out the additional flow cytometry investigations per annum (that is, additional recruitment would not be required). However, identification of a relatively large number of clinically significant non-SCID TCLs cases may present challenges in terms of the care pathways and clinical capacity for the management and treatment of non-SCID TCLs identified.

It was assumed that there is sufficient capacity for confirmatory testing of abnormal TREC screens within the current service in the Immunology Laboratory at St James's Hospital. However, this assumption is dependent on the TREC cut-off adopted following verification, which is typically set conservatively to reduce the risk of false negative results. As a potential consequence, identification of a relatively large number of non-SCID TCLs that may not be clinically significant and/or a high number of false positives may create a burden on flow cytometry services. If a decision is made to introduce TREC-based screening for SCID, consistent with standard practice in the NNBSP, provisional TREC cut-offs would need to be revised depending on review and evaluation of post-introduction testing outcomes (chapter 4). Therefore, testing protocols may present challenges for capacity during the early implementation period until protocols have been optimised.

Currently, newborns are screened for ADA-SCID with tandem mass spectrometry to identify ADA deficiency. Those identified with ADA-SCID may include cases of delayed-onset ADA-SCID for whom clinical onset is delayed, but who may present with less severe, but gradually worsening, immunodeficiency later in life. Patients with delayed-onset ADA-SCID may have normal TREC levels and therefore may not be detected by newborn screening (NBS) screening programmes including TREC-based screening only.[212] Therefore, while removal of ADA-SCID screening from the NBS programme may be associated with cost-offsets, it would also be associated with an increased risk of missing cases of delayed-onset ADA-SCID. In the context of the relatively high proportion of SCID cases in Ireland that are the ADA-SCID subtype, when compared with other countries internationally (chapter 3), a decision to remove ADA-SCID from the current panel may have small, but important clinical implications.

Although it may be possible to reconfigure the current NNBSL laboratory at CHI Temple Street to accommodate screening for TREC-based screening, this would be associated with an increase in the incremental budget impact. Whether or not it is considered reasonable to modify the existing laboratory would be dependent on a number of time-sensitive factors, including the potential lag time between decision-making and implementation, approval of funding, tendering and procurement, and the planned opening of the new children's hospital. A decision to implement SCID screening at CHI Temple Street, or to defer implementation until the laboratories are

operational at the new children's hospital, would be highly dependent on the estimated time to implementation and consideration of acceptable risk associated with deferring implementation (that is, the potential for missed cases during the intervening period). In addition, implementation decisions regarding other NBS conditions may influence the feasibility of implementing TREC-based screening for SCID at CHI Temple Street for assays where multiplex testing for a number of conditions may be possible (see also section 8.9).

Diagnosis and treatment

Diagnosis and treatment of SCID and non-SCID TCLs was associated with an estimated incremental budget impact of approximately €660,000, largely attributable to the costs associated with the potential identification of cases of SCID that are not diagnosed by current practice (that is, ADA-SCID screening, family history and clinical presentation). The rise in post-screening prevalence would reflect additional cases that currently go undiagnosed due to early mortality. The potential for an undiagnosed SCID population is highly dependent on the current standard of care in the country or region under consideration. As outlined in the systematic review in chapter 3, only one study conducted in the United States was identified that reported the change in prevalence following the introduction of TREC-based screening for SCID.[106] A 1.7 fold increase in the post-TREC-based screening prevalence was reported relative to the estimated pre-screening prevalence. However, this study was not considered directly applicable to the Irish context due to differences in the local epidemiology of SCID and the standard of care prior to screening being introduced.

In Ireland, current systematic screening for ADA-SCID as part of standard practice, and past targeted screening, mean the potential for an undiagnosed ADA-SCID population, specifically, may be lower relative to that in other contexts. Nonetheless, the available evidence from the US[106] and UK[101] indicates that the potential for an undiagnosed population cannot be ruled out, although the size of the population is subject to considerable uncertainty. In scenario analysis for the present BIA, the size of the undiagnosed population was varied between the upper and lower bounds of the plausible range based on the published literature. Uncertainty regarding estimates of the undiagnosed population had a significant impact on the incremental budget impact for part II. The base case assumed that there would be one additional SCID case diagnosed ever second year (post-screening prevalence of 1 in 28,468 births, based on mid-point of the upper and lower bounds of the plausible range). If there is no change in post-screening prevalence, introduction of TREC-based screening could be associated with a cost-offset of almost €30,000 over five years relative to current diagnosis and treatment practice costs; however, as noted, this is subject to considerable uncertainty.

An additional factor worth of consideration is that screening will detect SCID in seemingly healthy newborns. While being informed of a diagnosis of SCID will always be challenging for a family, it may come as less of a shock in those with a family history of SCID or where the infant presents clinically due to severe or recurrent infections. An unexpected diagnosis of SCID may therefore be associated with a significant psychological burden for the family who may require access to psychological support. Given the low incidence of SCID, it was assumed that any psychological support could be provided within existing resources, so no additional cost was included. The psychosocial implications of detecting SCID through screening are further discussed in section 9.2.1.

Limitations

Due to limitations in the available evidence, the results of this analysis are dependent on a number of assumptions. Where assumptions were subject to uncertainty, the validity of the estimated incremental budget impact was tested in sensitivity or scenario analysis to quantify the impact of methodological choices and modelling assumptions on the outcome. In particular, estimating the outcomes of screening prior to assay verification is challenging giving the dependence of testing outcomes on the TREC cut-off, methodology and algorithm used. However, given the rarity of SCID and non-SCID TCLs, despite the relative uncertainty associated with screening outcomes prior to assay verification, OWSA demonstrated that changes in the proportion of abnormal TREC screens within the plausible range are unlikely to translate into a considerable difference in the incremental budget impact.

The TREC assay demonstrates excellent sensitivity, but low specificity for the detection of SCID. As a result, the TREC assay can also detect newborns with non-SCID TCLs which are associated with aetiological and clinical heterogeneity. Various medical conditions and clinical circumstances have been reported to result in low TREC values in the absence of defined immune deficiency syndromes; these include prematurity, congenital syndromes, and cardiac or gastrointestinal complications, as well as idiopathic TCL (chapter 4).[213] For the purposes of this assessment it was assumed that SCID would account for 25% of all TCLs identified, based on estimates from the published literature. Given the uncertainty regarding the prevalence and clinical course of potential non-SCID TCLs, precise estimation of resource use associated with their management was not possible. Previous assessments have excluded the management of non-SCID TCLs given that the aim of TREC-based screening is detection of SCID;[77] however, this approach limits the interpretation of the net impact on the HSE of adding TREC-based screening for SCID to the programme.

For the purposes of this assessment, it was assumed that all equipment would be bought, rather than leased, as it was not possible to accurately estimate the leasing cost per test without engaging in a formal tendering process. Requesting quotes from suppliers prior to a decision regarding the introduction of a TREC-based screening for SCID being made was not considered appropriate. It is noted that leasing may be less costly initially and may be considered if the set-up costs in year one represent a barrier to implementation. Further considerations underlying financing decisions to lease or buy laboratory equipment are outlined in chapter 8.

As noted in section 7.2.4, with the exception of the previously undiagnosed population, this analysis considered the cost of management up to the point of HSCT. Currently, HSCT for SCID is provided in the UK at a fixed cost as part of the Treatment Abroad Scheme (TAS), irrespective of the clinical circumstances at the time of referral. In economic evaluations of TREC-based screening for SCID included in chapter 6, contingent on the assumptions underpinning the models, earlier compared with late HSCT was associated with improved patient outcomes, and thus a reduction in treatment costs.[101, 157, 189, 190, 194, 196, 197, 214-216] However, there was considerable variation in the magnitude of reported potential cost savings, ranging from a 29%[216] to 78%[190] reduction in the cost of HSCT. The repatriation of HSCT for SCID is the subject of a separate HTA which is currently underway to inform decision making by the HSE. However, even if HSCT is repatriated, it is unlikely that the evidence base would support precise estimation of potential cost offsets for a number of years, given low case numbers.

7.5 Conclusion

The estimated incremental budget impact associated with implementing TREC-based screening for SCID was €3.66 million over five years. Verification and implementation costs were estimated at €3.0 million, which was largely attributable to the cost of the TREC test kit (consumables) and setting up the laboratory. Treatment of SCID and non-SCID TCLs was estimated to be associated with an incremental budget impact of approximately €660,000, the majority of which was related to treatment of previously undiagnosed cases (that is, due to an assumed rise in post-TREC screening prevalence). The certainty of the results is limited by the availability of data to consider all relevant clinical and economic consequences. Key uncertainties include the cost of the TREC test kit, the number of abnormal TREC screens, care pathways for non-SCID TCLs and the incidence of undiagnosed SCID.

8. Organisational aspects of the addition of screening for SCID to the NNBSP

Key points

- The process of adding new conditions to the National Newborn Bloodspot Screening Programme (NNBSP) is complex and requires a collaborative and programme-centred approach. Implications specific to the potential addition of T-cell receptor excision circles (TREC)-based screening for severe combined immunodeficiency (SCID) to this existing programme are outlined under major topic headings with the work informed by the international literature and engagement with national stakeholders.
- While TREC-based screening for SCID would introduce a new technology to the National Newborn Bloodspot Screening Laboratory (NNBSL), it would not require a change to the current physical process of sample collection for screening.
- The capacity of the NNBSP (excluding laboratory specific requirements described below) is expected to suffice should the outlined needs of the current programme, which were submitted as part of the 2023 Health Service Executive (HSE) National Service Plan, be fulfilled.
- Implementation of TREC-based screening for SCID would require:
    - recruitment of additional laboratory staff to enable its verification and ongoing implementation
    - the introduction of molecular technology with associated equipment and training of laboratory personnel, given that this form of testing is not currently in place.
- The time at which screening is introduced would have important implications. The NNBSL is scheduled to move to the new children's hospital on the St James's Hospital Campus with extensive ongoing project management and resource requirements associated with this move. Samples for the NNBSP are currently processed at the NNBSL in Children's Health Ireland (CHI) Temple Street. If implemented at this site:
    - structural modification of the laboratory will be required to meet the additional physical space requirements for new sample handling and equipment

- the benefits of implementation will need to be considered in light of the upcoming move, taking account of the finite capacity for further project management.

- The testing method and screening algorithm will need to be established in terms of the defined screening target and establishment of population norms and cut-offs. Specific considerations for the screening algorithm include:
  - the handling of inconclusive results
  - provisions for infants that are preterm or in intensive care at the time of sample taking
  - review and revision of provisional TREC cut-offs set during assay verification, consistent with standard practice in the NNBSP
  - the sequence of the ADA-SCID screening test relative to the TREC-based screening test and whether the results of one test impacts the testing procedure or referral patterns of the other.
- If TREC-based screening for SCID is implemented, elements such as the communication of screen results, the structure of referral pathways, and the management of instances of false positives will need to be considered.
  - Screening for SCID will likely detect more cases of non-SCID T-cell lymphopenias (TCLs) than cases of SCID. This has implications for current HSE diagnosis and treatment pathways. While many of these non-SCID TCLs may be identified in the absence of screening, there will likely be additional demand on immunology services in terms of referrals for confirmatory diagnosis and follow-up appointments.
  - There are established diagnostic and treatment pathways for SCID. Follow-up of false positive results would be limited to one outpatient appointment for confirmatory testing, including a blood draw and subsequent communication with parents to relay the false positive finding and alleviate concerns. For non-SCD TCLs, follow-up would include outpatient attendance for confirmatory testing followed by initiation of clinical care appropriate to the condition detected.
- The NNBSP has an established quality assurance programme. As with any screening programme, ongoing monitoring and evaluation of outcomes will be

important. Specifically in the case of the addition of TREC-based screening for SCID, elements that may require consideration include the:

  - notably high uptake rate of the current NNBSP with near population-wide coverage. While international literature would not suggest that addition of screening for SCID would lead to a reduction in uptake, this indicator should continue to be monitored periodically.

  - outcomes associated with parallel testing for ADA-SCID as a result of both tandem mass spectrometry and TREC-based screening being in place. Monitoring of such outcomes would assist in future evaluation of the ongoing relevance of screening for ADA-SCID (in the context of TREC-based screening being in place).

- For conditions that meet the evidence bar for inclusion in the NNBSP, there may be efficiencies for the programme if implementation is deferred until a number of changes to the programme can be made at the one time rather than proceeding with sequential additions (that is, as soon as a positive recommendation is made). These efficiencies relate to the verification processes (particularly for conditions which may be screened for using the same technology), training requirements, and programme adjustments, with the upcoming move of the NNBSL to the new children's hospital being an additional consideration in terms of the timing of any changes. However, these efficiencies for the programme would need to be weighed against the individual clinical benefit for children identified through screening.

8.1 Introduction

The purpose of this chapter is to describe the organisational implications associated with the potential addition of T-cell receptor excision circles (TREC)-based screening for severe combined immunodeficiency (SCID) to the National Newborn Bloodspot Screening Programme (NNBSP) in Ireland. This chapter has been guided by the considerations outlined in the European network of HTA (EUnetHTA) Core Model organisational aspects domain.[14]

These potential organisational implications relate to changes to NNBSP current practice, laboratory requirements, the establishment of methods and algorithms, clinical pathways, follow-up capacity, quality assurance and evaluation, acceptability, and future newborn bloodspot conditions. While these implications have been outlined under individual topic headings, the procedure of adding a new condition to the NNBSP is a multi-tier and multidisciplinary process requiring a collaborative and programme-centred approach.[17] Additionally, it should be noted that a decision to

implement TREC-based screening may come at a time of limited capacity for the implementation of additional projects, in light of the finalisation of, and move to, the new children's hospital at the St James's Hospital Dublin campus.

8.2 Changes to NNBSP current practice

8.2.1 Sample collection

The process of sample collection is outlined in section 2.2.2. The implementation of TREC-based screening for SCID would use the same dried bloodspot (DBS) card and number of bloodspots as the current practice of the NNBSP, with no changes to the physical sample collection anticipated. Furthermore there are no changes anticipated in relation to the current responsibility for sample collection. The current levels of responsibility associated with sample collection are outlined by the NNBSP as follows:[18]

- Directors of Nursing and or Midwifery in maternity units and or hospitals are responsible for ensuring that all babies born in hospital are offered screening.
- Where informed consent is obtained:
    - hospital staff are responsible for either:
        - ensuring that the sample is taken prior to discharge or on return to the maternity unit / hospital
        - informing Public Health Nurses that a sample has not been collected.
    - Directors of Public Health Nursing are responsible for ensuring that the screen is carried out in their Local Health Area following notification from the maternity unit/hospital of babies residing in their designated area.

8.2.2 Novel technology

Screening for SCID would require the use of molecular testing, which is not currently carried out in the National Newborn Bloodspot Screening Laboratory (NNBSL) (see section 2.2). Specifically, the addition of SCID to the panel would require the use of real-time quantitative polymerase chain reaction (PCR), and a commercial assay kit capable of quantifying TREC levels in a DBS sample. As such, there will be requirements for the procurement of equipment, ensuring appropriate laboratory space, and training of laboratory staff (described in section 8.3 below).

8.2.3 Change to parent information

The NNBSP Governance Group is responsible for supporting the development of information resources and training for health professionals and parent(s) or guardian(s) regarding the NNBSP.[18] The publication *A Practical Guide to Newborn Bloodspot Screening In Ireland* (eighth edition, updated in May 2022) outlines the current process of information provision and responsibility for obtaining informed consent within the current NNBSP.[18] To facilitate the addition of SCID to the NNBSP, changes to the existing information relating to the programme would be required. These would include:

- the addition of a description of SCID to the information (written and verbal) currently provided to parent(s) or guardian(s) regarding the conditions screened for by healthcare professionals seeking consent for the heel prick test
- education material to be provided to the aforementioned healthcare professionals in the delivery of this information, as well as the ability to answer questions relating to SCID screening that parent(s) or guardian(s) may have during the consent process
    - It is anticipated that this will require a half day information update session on newborn bloodspot screening, which is considered to represent continued professional development.[204]
- changes to the HSE.ie landing page (and associated pages) for the programme
- changes to printed literature distributed in locations such as hospitals, general practitioner (GP) clinics, and other healthcare settings.

Given TREC-based screening for SCID will identify children with non-SCID T-cell lymphopenias (TCLs), consideration may need to be given to providing information to parents or guardians regarding these potential findings and their implications, alongside the potential for false positive tests. A detailed overview of considerations related to information provision and informed consent in this context is provided in section 9.3.2.

8.2.4 NNBSP resources

It was highlighted by the NNBSP Governance Group that it is not anticipated that the NNBSP itself would require additional staff if TREC-based screening for SCID were to be implemented, provided the current requirements submitted as per the Health Service Executive (HSE) National Service Plan are fulfilled.[204]

8.3 Laboratory considerations

A number of laboratory-specific considerations were identified and are outlined below, including equipment requirements, physical space requirements, recruitment, and training.

8.3.1 Equipment requirements

From the laboratory perspective, as outlined within the budget impact analysis in chapter seven, implementation of TREC-based screening for SCID would require the procurement of equipment and consumables (summarised in Table 8.1). Such equipment may be purchased at a capital investment cost or may be leased from the manufacturer. The approach adopted will impact how issues such as maintenance and depreciation are scheduled and costed. The decision as to whether to buy or lease equipment is beyond the scope of this assessment and will require engagement with manufacturers and relevant stakeholders to consider the benefits and limitations of each option.

Up to the time of writing, at least two commercially available, CE-marked kits for the quantification of TRECs have been described, namely: the Perkin Elmer EnLite Neonatal kit ™ and the Immuno IVD SPOT-it™ screening kit (formerly, the SCREEN-ID neonatal screening kit).[56, 57] These kits represent a consumable with the number used dependent on the number of births, the uptake of screening, and repeat sample requirements.

Table 8.1 Equipment and consumables requirements[204]

Laboratory equipment and consumable requirements	Estimated quantity
Real Time Polymerase Chain Reaction system	2
DBS puncher	2
TREC tests	Approximately 58,000 per annum*
Printers	2
Information and communications technology (ICT) configuration for SCID results	1
ICT interface to Specimen Gate	1

* Annual number will depend on birth rate, uptake rate, and repeat sample requirements.

8.3.2 Physical space requirements

Structural work and reconfiguration of the existing laboratory at Children's Health Ireland (CHI) Temple Street would be required if a decision was taken to implement TREC-based screening for SCID prior to the move to the new children's hospital on the St James's hospital campus. Specifically, laboratory staff have highlighted that

the floorplan of the existing NNBSL at CHI Temple Street is limited and cannot accommodate the additional equipment, and associated clean room, necessary for TREC-based screening for SCID. It was highlighted that an additional 24 to 30 m^2 of space would be required; this would comprise two rooms, one for sample preparation (to prevent contamination in the context of molecular testing) and the second for analysis.[204] Reconfiguration would require capital investment for structural modifications and personnel to project manage over an estimated six month timeframe (see chapter 6).

It was highlighted that there will be sufficient space and capacity to accommodate these requirements following the move of the NNBSL to the new children's hospital on the St James's Hospital campus in Dublin.[204] Consideration will need to be given to the timing of the implementation of TREC-based screening for SCID, should a positive recommendation be made.[204] Given the anticipated opening date of the laboratory at the new children's hospital in Q1 2025, the timeframe of the operation of TREC-base screening for SCID at the current Temple Street location could be very limited.[204] Furthermore, as highlighted previously, there may be a crowded project space given that laboratory staff are currently working on the planning and equipping aspects, alongside verification procedures, of the move, while continuing to provide services at the existing site.

8.3.3 Recruitment

Implementation of TREC-based screening would necessitate two phases: verification phase and ongoing implementation. The NNBSP identified that recruitment of one senior and one basic grade whole-time equivalent medical scientists for a period of nine to 12 months would be required to enable the verification of the testing method. To facilitate the implementation of testing at the population level on an ongoing basis, the NNBSP identified that two full-time equivalent basic grade medical scientists would be required. It should be noted that, at the time of writing, there is a documented shortage of medical scientists in Ireland which may impact such recruitment.[217]

8.3.4 Training of new and existing staff

As noted in section 2.2, should this screening programme be implemented it would introduce a new technology to the NNBSL. This would necessitate training for laboratory personnel, including both staff recruited specifically for this screening method and existing staff of the NNBSL, in order to enable cross-cover to occur.[204] The headcount of the NNBSL that would require such training, in terms of both current staff and additional staff to be recruited, is outlined in Table 8.2. While the two newly recruited staff would require training prior to the verification processes

taking place, it may be reasonable for other staff to complete the training in rotation over a period of months (for example, two every month). Furthermore, while formal training may be supported by the manufacturers in the initial phases, additional staff may be trained using a peer-to-peer cascade training approach.[204] It is anticipated that the required training will take up to five days per person.[204]

Table 8.2 Staff of the NNBSL requiring training[204]

Position	Whole Time Equivalent
Current staff	
Chief Medical Scientist	1.0
Senior Medical Scientist	3.0
Basic grade Medical Scientist	5.0
Recruited specifically for SCID: verification	
Senior Medical Scientist	1.0
Basic grade Medical Scientist	1.0
Recruited specifically for SCID: ongoing testing	
Basic grade Medical Scientist	2.0

Key: NNBSL National Newborn Bloodspot Screening Laboratory

8.4 Verify testing method and screening algorithm

As described in chapters two and four of this report, there will be a need to verify the testing method and screening algorithm. Such work is conducted prior to implementation of screening at the population level and will require additional resources from the laboratory perspective (as described in section 8.3.3 above). The procedure of adding a new condition to the NNBSP is a complex process requiring the input of multiple stakeholders and extensive verification in order to ensure the method performs to specification.[17] An example of the steps required for the recent addition of ADA-SCID was included in a previous HIQA report published in 2021, and is summarised in Appendix 8.1. Of note, this work related to the implementation of testing on an existing technology within the NNBSL (that is, tandem mass spectrometry); due to its novelty, TREC-based screening for SCID would involve greater complexity. The key considerations identified within this assessment are summarised in Table 8.3, with several expanded below.

Table 8.3 Considerations relevant to establishment of the testing method and screening algorithm

Considerations for TREC- based screening algorithm
Identification of appropriate TREC kit for use (including associated tendering process)
Definition of the target of screening
Establishment of TREC cut-offs
Use of immediate referral limits

Definition of criteria for repeat TREC tests
Criteria for repeat DBS requests
Handling of inconclusive or invalid results
Inclusion of pathways for preterm infants and those in NICU
Use of KREC assay in tandem
Sequencing and implications of ADA-SCID screening test result

Key: DBS – dried bloodspot, KREC - kappa-deleting recombination excision circle, NICU – neonatal intensive care unit, TREC – T-cell receptor excision circle

8.4.1 Definition of the targets of screening and verification of method

TREC-based testing is not specific to SCID, that is, TCLs other than SCID (non-SCID TCLs) will be identified, some of which will be clinically meaningful. The detection level of non-SCID TCLs for a given screening programme will vary depending on the TREC cut-off, screening algorithm, and diagnostic criteria in use.[50] International programmes differ in their perspective with some considering the primary target of the screening process to be SCID, with non-SCID TCLs considered to be secondary targets or incidental findings, while other programmes define the primary target as being any significant TCL.[218] If the primary target is SCID, the aim will be to ensure the TREC cut-off defined during initial verification does not miss cases of SCID (minimise false negatives) while remaining as specific as possible (minimise false positives – which may include clinically significant non-SCID TCLs). If the primary target is any significant TCL, a different TREC cut-off may be used.[58] The choice of primary target also has implications for the informed consent process (as outlined in section 9.3).Given the terms of reference for this health technology assessment (HTA), it was assumed that SCID was the primary target of screening. As with other conditions in the NNBSP, the primary target of this form of screening will need to be clearly defined in all communications.

While guidance may be provided by the manufacturer, there will be a need to establish and verify processes at the local level, including establishing population norms and test cut-offs, alongside referral pathways.[13, 24, 25, 58] As outlined in chapter four, the screening algorithms identified internationally have varied widely in terms of the TREC cut-offs used, control gene processes, and practices regarding repeat TREC testing of the same DBS, requirements for additional DBS samples, and the handling of inconclusive or invalid results. A number of sites were noted to use multiple TREC cut-off values, with lower limits triggering immediate referral and higher limits necessitating a repeat TREC test or a new DBS to be taken.[91, 104-107, 145] Such factors will need to be considered at the verification and implementation stages.

8.4.2 Consideration of prematurity and NICU admission

Evidence from the systematic review of TREC-based screening for SCID (chapter 4) identified that screening algorithms typically take account of gestational age and or neonatal intensive care unit (NICU) admission. Preterm infants may present with low T-cell counts which begin to normalise with gestational age, and hence, if screened within the standard timeframe may receive a true abnormal screen result which is not strictly meaningful.[51] However, infants who are born preterm may also have SCID and, therefore, it is important to include mechanisms to ensure these cases are still identified within the screening programme. Refinements to algorithms typically include a lower TREC cut-off or the request for a repeat DBS at corrected gestational age.[91, 104-107, 109, 145, 146, 149]

An additional consideration is the impact and timing of blood transfusions on the accuracy of screening test results which may be required for preterm infants or those in NICU.[146, 219] Standard NNBSP policy is for blood spot samples taken within 72 hours of a blood transfusion to be repeated.

8.4.3 Use of KREC assay

The scope of this HTA is to consider TREC-based newborn screening for SCID, and as such, the expansion of the testing method to include kappa-deleting recombination excision circle (KREC) quantification was not explicitly considered. However, as highlighted in section 2.5, four programmes internationally were noted to use combined TREC and KREC-based screening. The SPOT-it screening kit described above is equipped for both TREC and KREC quantification.[57] The quantification of KRECs can be used to identify infants that have significant B-cell lymphopenia, such as those with X-linked agammaglobulinemia. There is also some limited evidence to suggest that KREC-based testing may have added benefit in the detection of delayed- or late-onset ADA-SCID specifically.[50, 53, 54] However, it is noteworthy that within the national newborn bloodspot programme in Sweden, while TRECs and KRECs are measured in tandem, the KREC value is not considered in isolation for onward referral (that is, the infant must have evidence of TCL with or without B-cell lymphopenia); during pilot implementation increased false positivity rate were observed with referrals based on KREC counts alone.[55] Therefore, consideration should be given to the potential impact on referrals should the testing method be expanded to include KREC quantification.

8.4.4 Sequence and consideration of ADA-SCID screening results

As described in section 2.5, many international programmes have incorporated TREC-based screening for SCID. Less common however is use of tandem mass spectrometry to screen for ADA-SCID, with only screening programmes in Tuscany

(Italy), Catalonia, and Michigan (US) identified by the evaluation team as having introduced this form of screening for this subtype of SCID.[91, 95, 212] The use of tandem mass spectrometry to screen for ADA-SCID has been documented to detect cases of delayed-onset ADA-SCID that were missed by TREC-based screening; hence, this approach may mitigate the risk of cases being missed in TREC-based screening.[95, 212] ADA-SCID screening was implemented by the NNBSP in May 2022. In the event of a decision to also implement TREC-based screening for SCID, consideration will need to be given to the sequencing of these tests and whether the results of one impacts the testing procedure, or referral pattern, for the other.

8.5 Clinical pathways

An important consideration of any screening programme is its impact on clinical pathways. This may include the need to establish or modify existing clinical pathways, including those which relate to referral from an abnormal result and the diagnosis and treatment of a confirmed case.

8.5.1 Communication of results and referral pathways

Consistent with NNBSP processes for other screened conditions, the method of communication of positive screen results to parents and relevant healthcare personnel, and the initiation of referral pathways, will need to be explored. A case example may be drawn from the documented pathway for ADA-SCID screening,[204] whereby when an abnormal screening test result is identified, the Clinical Liaison Nurse in the NNBSL contacts the maternity hospital of the child's birth and requests that the parents are contacted as soon as possible to attend the hospital. Information about SCID, alongside a Parent Information Leaflet, is provided to parents at this stage by the local paediatric team. A repeat newborn bloodspot screening card and a 2ml sample of blood is requested for flow cytometry. The blood sample is taken by the local paediatric team and forwarded to the Immunology Lab at St James's Hospital for flow cytometry.

Pending the flow cytometry results, the infant is clinically evaluated by the local paediatric team and their interim clinical management is discussed with the Clinical Immunology Team at CHI Crumlin. Once reporting is complete, the flow cytometry results are provided to the referring hospital by the Immunology Lab in St James's Hospital who also informs the Clinical Immunology Team at CHI Crumlin by phone with a follow-up email confirmation. The Clinical Immunology Team at CHI Crumlin contact the local paediatric team, who inform the parents of the flow cytometry results. If an abnormal flow cytometry result is presented (that is, confirmation of TCL), a clinical management plan is agreed between the two teams and a plan is made for early transfer of the patient to CHI Crumlin.

The time interval from screening results to follow-up and confirmatory diagnosis is important, with a goal that this is as short as possible to reduce anxiety for the parents of the child, particularly when considering the potential instances of false positives (as discussed in section 9.2.3). As an example, an ongoing pilot of SCID screening in the UK has set 24 hours as the target for follow-up by an immunological team following an abnormal screen result.[58]

8.5.2 SCID diagnostic and treatment pathways

The goal of screening is to enable timely diagnosis and access to treatment. This is supported by evidence from the systematic review of the potential clinical benefits associated with early diagnosis and or HSCT compared with late diagnosis and or HSCT (chapter 5) which suggested that earlier treatment leads to improved outcomes for children with SCID. As described in chapter two, the HSE has defined clinical pathways for the diagnosis and subsequent clinical management of children with SCID. Should TREC-based screening for SCID be introduced, it is anticipated that the current standard of care and pathways can continue to be followed. However, consideration may need to be given to incorporation of performance indicators for elements such as follow-up appointments, referral times, and treatment access.

Other HTAs of TREC-based screening for SCID have emphasised the importance of prompt diagnosis and treatment following the screening test. For example, the Haute Autorité de Santé (HAS) in France recommended that diagnosis should be confirmed by one month of age to facilitate timely access to treatment, with a goal of transplant occurring by two months of age.[82]

8.5.3 Pathways for non-SCID TCLs

As noted, TREC-based screening is not specific to SCID, but will also lead to the identification of non-SCID TCLs. Given that a proportion of these cases are likely to be clinically significant and associated with persistent TCL, consideration of the pathways for diagnosis, follow-up and management for such cases will be required within decision-making on screening for SCID.[50, 62] While a proportion of these children would likely be identified in the absence of screening, it should be expected that screening will accelerate their entry to the health system with immediate demand placed on immunology services (as opposed to other services, depending on the presenting symptom or syndrome at the time of clinical identification).

As highlighted in chapter two, no guidelines for the management of these cases were identified within the international literature and previous reports have highlighted that there are currently no established consensus guidelines or algorithms for the management of non-SCID TCL cases detected through screening

programmes for SCID.[63, 64] Decisions surrounding the management of these non-SCID TCL cases are often made on a case-by-case basis, dependent on the signs and symptoms that are associated with the identification.[63]

8.5.4 Management of false positive cases

The NNBSP has established processes for communicating with and supporting parents, including processes for the communication of false positive results. Given that the programme already screens for a subset of SCID (that is ADA-SCID), it is unlikely that these processes will require significant change should a decision be taken to implement TREC-based screening for SCID. However, as identified in the systematic review of screening for SCID, timely and supportive communication of results is an important concern given evidence that parents of newborns continue to perceive their child as more vulnerable even after they are confirmed as false positive cases (section 4.3.8). This may indicate a need for support for such parent(s) or guardian(s) to alleviate concerns over the future health of the child (as discussed further in section 9.3).

8.5.5 Vaccination timing

As outlined in chapter 2, there are important interactions with the childhood vaccination schedule whereby children with a confirmed diagnosis of SCID or undergoing diagnostic testing should not be administered live viral or bacterial vaccines (for example, BCG and rotavirus), given the potential for severe illness and mortality in children with SCID.[9, 28] The ethical implications of a decision not to implement TREC-based screening for SCID in this context are discussed in section 9.2. In Ireland, the rotavirus vaccine is part of the HSE's recommended primary childhood immunisation schedule with the first dose given at two months of age, which would typically be before the onset of clinical symptoms for a child with SCID (as described in section 3.3.1).[29] If TREC-based screening for SCID were to be introduced, an infant will likely be identified with SCID or undergoing investigation for SCID prior to this age. Adapted vaccinations pathways may be required should there be concerns that the results of the screening pathway will not be known prior to administration of live vaccines, or for example, if there was a decision to add additional live vaccinations to the immunisation schedule. It should also be noted that in the absence of national electronic health records, there is a reliance on information provided by the family and or timely communication between healthcare professionals to ensure vaccinators are aware of screening test results.

8.6 Follow-up capacity

Beyond laboratory-specific constraints, a number of additional capacity considerations were identified with regard to referrals for flow cytometry and for clinical appointments.

8.6.1 Flow cytometry referrals

As outlined in chapter 2, infants with an abnormal TREC-based screening result would be referred onwards for flow cytometry as part of confirmatory testing. Consideration will need to be given to the capacity for these referrals should a decision be made to add TREC-based for SCID to the current NNBSP. The infants referred will include children with SCID, non-SCID TCLs, and instances of false positives from the initial TREC test. From the systematic review summarised in chapter four, the median percentage of children reported across the included studies as requiring flow cytometry on the basis of an abnormal screen result was 0.03% (range 0.01% to 0.12%); based on the expected annual birth cohort in Ireland, this would equate to 17 cases (ranging from 4 to 72) per annum. Currently, there is one laboratory in Ireland performing flow cytometry for suspected SCID cases (St James's Hospital, Dublin). From the international ranges reported, it is not anticipated that the addition of TREC-based screening for SCID would require any additional resources, with the laboratory staff indicating that there should be capacity to facilitate additional referrals with the currently available equipment and personnel.[211] However, should a positive recommendation be made, and should substantially more referrals be anticipated based on the verification and implementation work completed at the local level, the available resources and capacity may need to be reconsidered.[211]

8.6.2 Appointment capacity

As noted in chapters two and four, TREC-based screening will identify SCID cases and non-SCID TCLs of a diverse nature. The rate of detection will depend on the screening algorithm and cut-offs applied during laboratory verification; however, a proportion of these infants will require follow-up with the paediatric immunology team at CHI Crumlin, with some requiring multiple appointments, long-term follow-up, and ongoing intervention. As noted in section 8.5, some of these children will be identified in the absence of screening; however, screening would place an immediate demand on the immunology team. Based on the international ranges reported in chapter 7, the CHI immunology team has indicated that should screening be introduced no additional resources would be required given the currently available personnel. However, consideration would need to be given to the clinical

appointment capacity to ensure that it is sufficient to meet the demand, and to ensure that other care is not displaced.

8.7 Quality assurance and evaluation

8.7.1 Programme standards and quality assurance

The NNBSP Governance Group, in partnership with health professionals and parents, is responsible for coordinating, the NNBSP quality assurance programme as well as monitoring and facilitating improvements to the programme.[18]

Establishing programme standards and ensuring the standards are met by regular evaluations are important considerations for organised screening programmes.[15] Quality assurance strategies embedded within a programme facilitate formal evaluation. The WHO has specified that quality assurance systems for effective screening programmes have various components, including the following:

- standards based on the parameters of the programme
- a system to check that the standards are being met
- guidance and operational policies
- mechanisms to ensure the quality of the testing
- failsafe systems
- quality improvement initiatives to support services to improve their quality.

These components are discussed below in the context of the potential addition of TREC-based screening for SCID to the NNBSP.

1. Standards setting

In screening programmes, most quality standards measure processes in the screening pathways such as uptake rate, as well as structural aspects of the programme, such as laboratory standards.[15] Performance measurement in the context of addition of SCID could be enabled by development of quality standards with key performance indicators (KPIs) addressing the following areas:

- programme uptake rate (specifically any changes to the current NNBSP uptake rate following the addition of TREC-base screening for SCID)
    - The NNBSP currently has notably high national participation in the programme overall at an estimated 99.9%.[19] It will be important that

any amendments to the current programme does not impact this high participation rate.(86)

- test performance
    - In terms of the test performance, key indicators include the sensitivity and specificity of the test in addition to the positive predictive value (PPV) and negative predictive value (NPV). As described in chapter four, performance values for these measures depend on test methodologies, cut-offs and algorithms in place; however, these will need to be determined and regularly monitored. The documented experience of introducing newborn screening for SCID in New Zealand highlights that consideration may need to be given to different screening metrics for SCID and other clinically significant TCL (for example, consider PPV for SCID and TCL (including SCID) separately).(220)
- communication of findings to parents and compliance with further diagnostic testing
    - It will be important to ensure that all parents of children with an abnormal screen result are contacted in a timely matter, consistent with the clinical pathways described above and in chapter two, and that follow-up and referral pathways are initiated and completed for all identified infants.

2. Checking that standards are being met

Following the development of any additional standards required following the addition of TREC-based screening for SCID, regular measurement of these will be important. As the NNBSP is an established programme, with established quality control measures, current processes for governance and responsibility can likely continue to be followed once any SCID-specific amendments have been introduced.

3. Guidance and operating policies

Consideration should be given to the need for the policies for guidance and operation to describe in detail any changes required to the delivery of the programme in the context of the addition of TREC-based screening for SCID.(15) The following documents may need to be reviewed and updated:

- HSE landing page for the NNBSP website
- parent information leaflets, including translations

- training modules such as those hosted on HSE's online learning and development portal 'HSELanD'
- 'A Practical Guide to Newborn Screening in Ireland'
- sample takers' guide
- HSE Standard Operating Procedure.

4. Mechanisms to ensure the quality of the testing

The quality of the testing itself will also require monitoring.[15] New equipment purchased or leased should be maintained in accordance with existing laboratory procedures. In line with existing laboratory policy, quality control and quality assurance processes should be adhered to with all laboratory procedures in compliance with ISO 15189 (the international standard for requirements for quality and competence within medical laboratories).

5. Failsafe system

Failsafes are back-up measures to mitigate potential errors in the screening programme.[15] Any additional failsafe systems required for TREC- based screening for SCID specifically should be explored. There are multiple agencies and groups responsible for ensuring testing is offered to all infants and that screening is carried out appropriately within the NNBSP.[18] These responsibilities are not anticipated to be impacted by the addition of TREC-based screening for SCID specifically.

6. Quality improvement initiatives

If TREC-based screening for SCID is implemented, training of staff will be required. Consideration should be given to the need for cyclical training of staff to ensure that the appropriate education is provided for those that require it, and that learning is refreshed at regular intervals in accordance with existing medical laboratory standards. In terms of DBS sample takers and clinical staff, measures may be required to ensure that new information is circulated regarding the NNBSP including any changes to current processes arising from amendments to the programme.

It may also be pragmatic to assess outcomes of parallel testing for ADA-SCID using tandem mass spectrometry and TREC-based screening for all SCID subtypes following implementation to ensure the testing processes are being performed as efficiently as possible.

8.8 Acceptability

The acceptability of a screening programme is an integral consideration within decision-making, as evidenced by criteria set out by Wilson and Junger,[221] the World Health Organization (WHO),[15] and the National Screening Advisory Committee (NSAC) in Ireland specifically.[16] Acceptability of any national screening programme is important to the uptake rate of the programme, which is in turn important to the viability and success of the programme itself. Currently the NNBSP has an estimated uptake rate of 99.9%.[19] Similarly high uptake rates (≥98%) were outlined in four out of five cohorts screened for SCID specifically, as described in chapter four.[55, 105, 147, 159] In 2022, Rare Diseases Ireland (RDI) published the results of a survey examining public awareness and opinions on newborn bloodspot screening in Ireland. Results of the survey indicated that, of those surveyed (n = 1,000), 62% thought that the programme should be screening for as many conditions as possible, while a further 15% supported screening newborns for the most severe conditions only. While not specific to SCID, these figures suggest there is a potential ongoing support for the expansion of the programme generally; however, it should be noted that 9.3% of those surveyed (n = 93) were adults living with rare conditions; the sample is therefore not representative of the overall population.[222]

A 2021 pilot study completed in the Netherlands provides a detailed overview of parent perceptions of newborn screening for SCID.[146] The study found that the majority of parents surveyed supported newborn screening for SCID.[146] Parents' support was outlined from both public health (mean rating 4.3/5) and personal perspectives (mean rating 4.2/5).[146] In terms of reasons provided for participation in newborn screening for SCID, the following were expressed: the potential health benefit for their child; to support scientific research; that no extra blood had to be drawn; that the disorder can be cured; and to help other children.[146] While the majority of parents supported, and accepted participation in, newborn screening for SCID, the authors found that for the minority who did not there was a tendency to have a more pessimistic attitude towards scientific research generally, and some cited not considering SCID to be an important addition to the current programme.[146]

A further study from the Netherlands examined, through interviews, the perspectives of stakeholders on the expansion of newborn bloodspot screening.[223] The study included policy-makers/institutions (n = 8), parents and patient organisations (n = 18), healthcare professionals (n = 9), and representatives from research and test and therapy development (n = 4).[223] The study found that both professionals and parents had a positive attitude towards the expansion of the current newborn

screening (NBS) programme, as highlighted in a recommendation document published by the Health Council of the Netherlands, which included the addition of SCID screening to the programme.[224]

The reputation and acceptance of the current programme should also be taken into consideration. The notably high uptake rate of the current NNBSP indicates near population-wide coverage;[19] therefore, any potential harm to the trust and confidence in the NNBSP as a result of the introduction of TREC-based screening for SCID, alongside any other conditions added in the future, should be considered. Processes for dealing with false positives and potential false negatives should be explored to maintain confidence in the programme (see section 9.2). Furthermore, as TREC-based screening for SCID is not necessarily specific to SCID, consideration will need to be given to how the test is described and how the results are communicated to parent(s) or legal guardian(s) (see section 9.3). As suggested by the WHO, ongoing monitoring and evaluation of coverage and uptake of the programme would help to identify if a decline was experienced following an amendment to the programme.[15]

8.9 Addition of future newborn bloodspot conditions to the NNBSP

As outlined in chapter 2, TREC-based screening for SCID is performed by quantification of TREC using PCR. Screening for other conditions may also be undertaken using PCR technology, such as, for example, screening for Spinal Muscular Atrophy (SMA) by qualitative detection of exon 7 of the *SMN1* gene. As such, an initial capital investment in screening for SCID may provide downstream reductions in the investment required should additional conditions using the same platform be added to the NNBSP. Furthermore, as in the case of SCID and SMA, multiplex test kits that permit simultaneous screening for two or more conditions may be commercially available, which may result in lower incremental costs compared with use of separate test kits for each condition.[225]

For newborn screening generally, consideration should be also be afforded to the sequence that conditions for which screening has been recommended are added to the NNBSP, given the extensive verification and implementation work associated with each addition. As highlighted within the budget impact analysis (BIA) in chapter six of this report and throughout this present chapter, the addition of a condition to the NNBSP is associated with considerable burden from the perspective of the programme as a whole and for the laboratory in particular. For conditions that meet the evidence bar for inclusion in the NNBSP, consideration of the timing of these additions may provide opportunities to facilitate efficiencies in the verification processes, training requirements, and programme adjustments. However,

efficiencies for the system would need to be weighed against the clinical benefit for children associated with implementing changes sequentially (that is, as soon as a positive recommendation is made) rather than delaying implementation to allow for a number of changes to be made at the one time.

8.10 Discussion

The purpose of this chapter was to describe the organisational implications associated with the potential addition of screening for SCID to the NNBSP in Ireland. The information presented has been collated following engagement with stakeholders from the NNBSP, NNBSL, and the clinical perspective, alongside examination of the international literature for TREC-based newborn screening for SCID.

Key considerations relevant to decision-making have been presented and framed in the context of the various stakeholders and systems that may be impacted should this form of screening be introduced, alongside the resources that are likely to be required. Again, it should be emphasised that while these considerations have been outlined under individual topic headings for ease of interpretation, the procedure of adding a new condition to the NNBSP is a multi-tier and multidisciplinary process requiring a collaborative and programme-centred approach.[17]

Throughout the completion of this HTA, a number of contingencies have been identified which are likely to impact on the feasibility of TREC-based newborn screening for SCID, should it be recommended, that should be borne in mind during decision-making. These include the:

- capacity of the NNBSP to implement this form of screening considering the requirements submitted to the HSE National Service Plan
- recruitment and training of NNBSL staff to enable verification and subsequent implementation at the population level
- procurement of equipment and consumables for testing
- structural reconfiguration of the NNBSL at CHI Temple Street Dublin to facilitate physical space requirements should implementation be initiated while at this location
- timing of such implementation relative to the planned move of the NNBSL to the new children's hospital on the St James's Hospital Dublin campus including the laboratory capacity at that location

- number of referrals for flow cytometry remaining in line with those estimated from international sources and not exceeding current capacity.

There are a number of laboratory-specific considerations outlined that would require engagement with relevant stakeholders to discuss the assumed benefits and limitations of various options and to decide on the best considered course; these include: the site of implementation of screening and the approach to procurement of equipment. In terms of the site of implementation, consideration needs to be given to whether the NNBSL at CHI Temple Street should be structurally configured to facilitate screening, versus delaying the implementation until the laboratory has completed its move to the new children's hospital. Depending on the expected completion dates, this reconfiguration could be completed to facilitate a relatively short time period of verification and testing. Additionally, it may come at a time when capacity overall is finite given the project requirements of moving to, and setting up, the new NNBSL. However, such considerations should be balanced against the potential clinical impact of delaying implementation. In terms of the procurement, there will likely be an option to lease as opposed to buy the necessary equipment at a capital cost, with the cost dispersed across each individual test. The approach adopted will impact how issues such as maintenance is scheduled and costed.

The addition of TREC-based newborn screening for SCID to the NNBSP appears highly reliant on the recruitment of medical scientists to the NNBSL to enable verification, implementation, and ongoing testing at the population-level. As noted, at the time of writing, there is a documented shortage of medical scientists in Ireland which may impact such recruitment, and hence implementation, should a positive recommendation be made.[217]

While all amendments to screening programmes pose challenges, the introduction of novel technologies and testing methods within a programme presents additional complexities. These were documented during the implementation of newborn screening for SCID in New Zealand secondary to elements such as space requirements, training, and quality control.[220] This type of testing raises another unique consideration when compared with other tests in the programme in that screening for SCID includes the analysis of DNA in the initial screening test (albeit, what is actually being screened is an absence of a DNA by-product).[226] Given that DNA analysis has historically been associated with public caution, a 2021 publication from the UK, where SCID screening is currently under pilot, suggested that public consultation may be necessary to alleviate potential fear or anticipation associated with mass DNA screening.[226] This element may require consideration in terms of information provision and processes for informed consent (section 9.3)

Once the testing method and screening algorithm have been established, ongoing appraisal of their efficiency and refinement will likely be required as evidenced by studies in chapters two and four reporting adjustments to the TREC value used over the course of the study period,[55, 91, 104, 108, 145, 146] with all but one lowering the cut-off.[146] These refinements were typically due to an excess number of referrals for confirmatory testing and or identification of cases deemed not to be clinically meaningful. When considering preterm infants and those in NICU, pre-evaluation work from an ongoing pilot of screening for SCID in the UK indicated that not having a separate pathway for preterm infants within the screening algorithm would result in large numbers of false positive results potentially overwhelming immunology services.[58] Furthermore, a 2022 publication documenting the experience of implementing newborn screening for SCID in New Zealand highlighted a 35-fold difference in out-of-range results for samples from NICU compared with community samples, which was associated with challenges in the screening algorithm and diagnostic referrals.[220]

8.11 Conclusion

The process of implementing TREC-based screening for SCID, and its embedding within the existing NNBSP, will require a collaborative and programme-centred approach. Should a positive recommendation be made, the implementation of this form of screening would necessitate capital investment, recruitment, laboratory verification, and amendments to the current processes of the NNBSP. There are a number of contingencies that should be considered, including the capacity of the laboratory (in terms of equipment, training, physical space, and personnel), and the clinical pathways (in terms of referrals for diagnostic testing and follow-up). As with other additions to the NNBSP, potential changes to the screening panel need to be considered and managed within the context of the overall delivery of the programme to ensure its continued coherence.

9. Ethical and social considerations associated with the addition of newborn screening for SCID

Key points

- This chapter sought to outline the potential ethical and social considerations associated with the addition of T-cell receptor excision circles (TREC)-based screening for severe combined immunodeficiency (SCID) to the National Newborn Bloodspot Screening Programme (NNBSP) in Ireland. The chapter is structured by four main topic areas: benefit-harm balance, autonomy, justice and equity, and ethical consequences of the HTA.
- The benefit-harm balance differs between and within the multiple groups that may be detected. There is clear benefit for children with SCID in terms of improved clinical outcomes, no benefit for those identified as false positives, and variable potential to benefit in the case of non-SCID TCLs identified.
    - For those with an abnormal test, screening has further potential benefits (for example, reduction in diagnostic odyssey) and harms (for example, stress and anxiety relating to instances of false positives) for the parents and family of the child involved.
    - International studies have noted the importance of providing information in a clear, consistent and timely manner in the context of an abnormal screening test result. The method of communicating such results should therefore be considered in terms of its potential to impact on the parents and family of the newborn.
- Screening has implications for population engagement and trust with each of the NNBSP and the childhood immunisation programme in Ireland. Children with SCID should not receive live vaccines; in the absence of screening, it is possible that a live vaccine could be administered to the child's detriment. Such an event may also result in a loss of confidence in the programme and a reduction in uptake in children for whom vaccination is safe and beneficial.
- With regards to autonomy, screening for SCID involves a particularly vulnerable population (newborns) with consent provided by parents, potentially at a time of stress and fatigue in the postnatal period. Obtaining truly informed consent in the context of newborn screening can be challenging given the

rarity and complexity of the conditions screened, alongside the intricacy of understanding screening processes themselves.

  - Given the relatively unique scenario in Ireland, consideration will need to be given to how information would be provided and consent obtained in the context of screening for all SCID subtypes and ADA-SCID specifically given these use separate tests.

  - Careful balance is required to not overstate the potential for positive findings while still ensuring the parent is informed of the potential outcomes and impact of screening, particularly when considering the range of non-SCID TCLs that may be detected.

  - The influence of socioeconomic factors and health literacy has further important bearing on how information is provided and translated into parent decision-making.

- From the perspective of justice and equity, there is a potential for displaced care and strain on the capacity of the system, should this form of screening be implemented, which may not be equitable at the population level. This is particularly relevant when considering the number and types of non-SCID TCLs that may be detected, and is further compounded by the uncertainties that exist in the estimates of cost effectiveness and resource implications associated with the addition of TREC-based screening for SCID to an existing programme that screens for a subtype of SCID, that is ADA-SCID.

  - Additionally, there are parental factors that may impact the ability of the newborn to access screening. These factors may have ongoing impact when considering the newborn's ability to access follow-up care in the case of positive screen results.

- In terms of the ethical consequences relating to the conduct of the HTA itself, there are limitations in the evidence available nationally and internationally to inform these types of assessments; many estimates included within the HTA are based on proxies, expert opinion, or are associated with much uncertainty.

  - There are also important considerations relating to the timing of the HTA and the impact on overall findings in light of elements such as the recent addition of ADA-SCID screening to the NNBSP, the ongoing expansion of newborn bloodspot screening programmes, and the current assessment of HSCT repatriation.

9.1 Introduction

The purpose of this chapter is to describe the ethical and social considerations associated with the potential addition of T-cell receptor excision circles (TREC)-based screening for severe combined immunodeficiency (SCID) to the National Newborn Bloodspot Screening Programme (NNBSP) in Ireland. This chapter has been developed broadly in line with the structure described in the European network of HTA (EUnetHTA) Core Model and incorporates two domains of assessment: ethical analysis, and patient and social aspects.[14] Generally, the ethical issues relating to a technology should be assessed with reference to the prevalent social and moral norms relevant to the technology, and also with respect to the Health Technology Assessment (HTA) itself (for example, the time at which a HTA is conducted). The main topic areas described in this chapter relate to five pillars of the ethical analysis domain, with the patient and social perspective discussed under these topic headings, where appropriate:

- benefit - harm balance
- autonomy
- respect for persons
- justice and equity
- ethical consequences of the HTA.

9.2 Benefit – harm balance

Screening for SCID involves testing a large population of newborns annually (that is, all newborns whose parents consent to screening), in order to identify a small number of children with SCID (approximately 1-2 cases annually). With any population-based screening programme, it is important to consider the distinction, between the individual and the population, and where the balance of benefits will lie.[14] As the addition of TREC-based screening for SCID would constitute an expansion of an existing screening programme focused on rare diseases, ethical concerns regarding the testing of a large population to detect a small number of cases are not considered to be overly contentious in the context of this assessment.

While screening for SCID likely confers benefits on the child with SCID and their family, the screening test will also detect other congenital and secondary causes of T-cell lymphopenia (TCL), termed ‘non-SCID TCLs’. As with any screening test, there is also potential for false positive and false negative results. Therefore, it is important that each potential outcome is discussed in terms of the benefit to harm balance associated with screening.

9.2.1 Children with SCID

As discussed in chapters two, three and five, there are clear clinical benefits to the child with SCID in terms of its early identification: it enables earlier access to definitive treatment for the condition (haematopoietic stem cell transplantation (HSCT)) and avoidance of live vaccines thereby reducing the risk of complications and leading to improved clinical outcomes. Beyond clinical outcomes, there are likely to be further benefits for the family unit, and subsequently the child, in terms of a reduced diagnostic odyssey. The term 'diagnostic odyssey' is used to represent the uncertain and often unpredictable time from initial presentation with clinical symptoms suggestive of a person's condition to receiving a definitive diagnosis. The odyssey may be characterised by its duration and its circuitousness (number of consultations or different specialities involved) from beginning to end and can be associated with stress and anxiety for the family.[227] In the absence of screening, or a known family history, the diagnostic odyssey for SCID may begin with the child presenting at approximately three to six months with recurrent and often severe infections for which a cause is not immediately clear. While a short time period will remain between receipt of a screening test result and diagnosis (following confirmatory testing), screening largely eliminates the diagnostic odyssey with the exception of where a false negative screening result is received; however, as described below, these are considered rare in the context of screening for SCID.

From a timing perspective, following a positive screening test result, there will be a need for the child to attend medical appointments for confirmatory diagnosis and follow-up in the early weeks of life, which may interrupt the family-child bonding period; this experience may be contrasted with the experience of receiving the diagnosis later in the child's life. Furthermore, while screening may infer earlier diagnosis and access to treatment, this in turn implies earlier interruption of family life, separation from the child for investigations (for example, if a parent needs to work), and potentially earlier travel to the UK (for HSCT). These factors are likely to be associated with social and financial impact on the parents and family. While these considerations will be present once a diagnosis of SCID has been made, regardless of whether screening has taken place, they will be accelerated in the context of screening and occur earlier in the postnatal period; this may be more difficult for the family to reconcile than if they were to occur a number of months after birth (in the absence of screening). However, in the context of SCID being a life-threatening condition, these potential harms are likely to be far outweighed by the clinical benefit associated with earlier diagnosis and treatment.

9.2.2 Children with non-SCID TCLs

TREC-based screening is not specific for just SCID so it will also identify other TCLs, some of which may be clinically significant. Screening for SCID is likely to detect a higher number of children with non-SCID TCLs than children with SCID (see chapter 2 and chapter 4). A wide range of potential non-SCID TCL causes have been documented as being detected during newborn screening for SCID. These include congenital syndromes (such as 22q.11 Deletion Syndrome), secondary causes (such as congenital heart disease), and those which are idiopathic in nature (which may be transient or persistent). The detection level of such non-SCID TCLs will vary depending on the TREC cut-off, screening algorithm, and diagnostic criteria in use.

The challenges associated with the detection of non-SCID TCLs in newborn screening for SCID have been debated internationally.[147, 218, 228] While appreciating the categorisation may be influenced by the perspective chosen, the authors suggest that a distinction may be drawn between 'actionable' and 'non-actionable' non-SCID TCLs identified. Actionable findings are considered to be causes for which the identification of the child leads to earlier treatment or preventative strategies which may result in substantial benefit. These children may benefit from prophylaxis, infection prevention and control (IPC) measures, avoidance of live vaccines, and access to earlier treatment. Furthermore, there may be benefits in terms of minimising the diagnostic odyssey and informing future family planning. In the context of screening for SCID, non-actionable secondary findings are those which may be relevant in terms of understanding prognosis, but for which no treatment options are available or where such options have limited or uncertain impact on overall outcomes (for example, treatment being limited to supportive therapies).[218, 228] Such non-actionable secondary findings have further implications for healthcare resources and clinical capacity. Depending on the perspective taken, non-actionable findings may include idiopathic TCLs which are often unpredictable in their course, may be transient in nature and present a risk of overtreatment. An example of a notably more severe condition which may be identified as a result of screening for SCID, and which has been discussed within the literature, is ataxia telangiectasia. This condition presents asymptomatically at birth, does not have a curative treatment available, and the benefits of its identification through screening are considered to be unclear.[77, 228] Notably, parents identified as carriers of the genetic mutation associated with ataxia telangiectasia have been found to be at risk of developing certain cancers including breast cancer.[228] Therefore, there is the potential for newborn screening to expose further health complications for the family beyond that of the newborn; this may be viewed as a benefit or a harm depending on the context and viewpoint taken.[228]

In terms of the diagnostic odyssey, there may be a case for earlier diagnosis of certain non-SCID TCL conditions as detection through screening may reduce the diagnostic odyssey for some families. However, there will also be children identified for whom a definitive cause for their TCL cannot be readily established. In such cases, screening could potentially increase or accelerate the odyssey, thus inferring a potential harm. As with SCID, these children will require ongoing testing and investigations which may impact on the family as a whole in terms of disruption, separation, and emotional distress. Conversely, this early entry to the process of testing and investigation may be viewed positively in reducing parental anxiety and doubt should a child eventually present with symptoms, even if a definitive cause cannot be established.

Specifically in the case of preterm infants, careful consideration is required regarding their management within screening algorithms for SCID. As outlined in chapter 2, preterm infants may present with low T-cell counts which begin to normalise with gestational age.[51] This cohort may therefore receive abnormal screening test results that are not clinically meaningful causing unnecessary anxiety and stress for parents in addition to the worry experienced over the health of the child due to their prematurity. However, it is important to consider that preterm infants may also be diagnosed with SCID and, therefore, mechanisms are required to ensure their identification is balanced in the consideration of the potential for benefit and harm.

9.2.3 Instances of false positives

All screening tests are typically associated with false positive results (that is, some people without the condition being screened for will receive a test result saying the condition has been detected). In the context of screening for SCID, such instances of false positives represent a harm without any benefit to the child or family. These children will require clinical examination and a blood draw for confirmatory testing through flow cytometry which, albeit a minor invasive procedure, still represents an unnecessary medical procedure and an inefficient use of healthcare resources.

Aside from unnecessary medical tests, instances of false positives may be associated with considerable psychosocial burden on the family. In the immediate term following a positive screening result, there may be stress and anxiety experienced over the potential that the newborn has a serious health condition; the occurrence of such stress and anxiety has been documented in newborn screening (NBS) programmes generally,[229, 230] and in screening for SCID specifically.[146] Furthermore, as described above, there is a need to interrupt the initial bonding period in the initial weeks of a newborn's life to complete confirmatory testing. This interruption may impact on family-child bonding at a particularly crucial stage in the lifecycle, resulting in regret over time lost, though this has previously been noted to

not be a long-lasting disruption in NBS programmes generally.[229] While the benefits of screening may outweigh the harms for children with SCID and for certain cases of non-SCID TCLs, the potential harm to children who are subsequently identified as false positive cases should be considered. Specifically in screening for SCID, pilot data from the Netherlands noted that some parents of newborns continued to perceive their child as more vulnerable even after they were confirmed as false positive cases.[146] In this context, the time period from receipt of a positive screen result to receipt of confirmatory test results is likely impactful and, ideally, should be as short as possible.

It should be highlighted that while this emotional distress is impactful for the family, results from the above pilot study in the Netherlands indicated that, for the majority, their trust in the NBS programme was not changed by the experience.[146]

9.2.4 Instances of false negatives

While cases of false negative test results are considered to be rare in the context of screening for SCID,[50] they do exist (that is, rarely a child with the condition will receive a test result saying the condition has not been detected). In all contexts, there is the potential for harm associated with false negative results. For example, there may be delays in the receipt of diagnosis, limiting the ability to prevent complications and initiate definitive treatment. These delays may arise if diagnostic evaluation is drawn away from the true condition due to a false reassurance of clinicians and families afforded by the negative screening result.[231]

As described in chapter four, a limited number of missed cases have been reported from evaluations of population-based screening programmes in the US.[104, 154] These documented missed cases have largely related to those with leaky or delayed-onset SCID. In contrast with delayed-onset SCID, typical SCID patients present early in life with severely depleted levels, or an absence, of T-cells; typical SCID is likely to be detected regardless of the threshold used. As described in section 3.3.1, delayed-onset SCID is associated with later onset of symptoms with delays in diagnosis and subsequent intervention and as result is associated with increased risk of infectious and non-infectious complications that may impact on clinical outcomes for the child.[232, 233] As documented in section 2.2, the NNBSP currently screens for a subset of SCID, that is, ADA-SCID, using tandem mass spectrometry (MS/MS). There is evidence that cases of delayed-onset ADA-SCID missed by TREC-based screening are detected by MS/MS screening.[95, 212] Therefore, while all screening programmes are associated with an intrinsic risk of false negatives,[234] the current NNBSP strategy of screening for ADA-SCID may mitigate this risk in the context of the addition of TREC-based screening.

9.2.5 Communication of screening results

The way in which abnormal results are communicated has been noted to impact on parents' screening experience.[146, 230, 235] Receipt of an abnormal screening test results can be a source of stress and anxiety for parents, and strategies to mitigate these factors should be considered. For example, data from a pilot study of SCID screening in the Netherlands indicated that parents of children with an abnormal screening result frequently noted dissatisfaction with communication of results, highlighting that they either received too little or incorrect information from the general practitioner (GP).[146] Parents expressed a preference to be contacted by a paediatric immunologist directly rather than receiving initial counselling from the GP, so they could receive correct and clear information with the opportunity to ask questions.[146] In the initial contact period, results from a qualitative study in the UK on NBS screening indicated further areas for improvement; these included recommendations for the development of exemplar communication scripts for the first call to parents, direct contact between a specialist and the family the same day the parents are notified of the abnormal screening result, access to advice and support during the period spent waiting for an appointment with a specialist, and the development of information related to true and false positive results.[235]

Considering false positive screening results in particular, it would appear pragmatic that consideration is given to the communication of confirmatory test results to parents in a manner which offers reassurance and provides opportunities for the parents to ask questions and discuss concerns over the future health of the child.

In terms of the communication of 'not suspected' screening test results, the method of informing parents varies. In Ireland, if there is no requirement for follow-up testing from the NNBSP, then the parent is not currently contacted further, and hence it is assumed that the test has not shown an abnormal result.[18] In the UK, parents are informed of all test outcomes, including a 'not suspected' result.[236] In terms of closing the communication loop and alleviating any potential concern or anxiety about test results, consideration could be given to a policy of informing parents of all test results.

9.2.6 Trust in NNBSP and childhood vaccination programme

As highlighted in chapter 8, the current almost universal uptake (estimated at 99.9%) of newborn bloodspot screening in Ireland suggests a level of confidence in the NNBSP which is important to maintain. However, instances of false positives, identification of `non-actionable' non-SCID TCLs, and false negatives present a potential risk to the current programme in terms of undermining trust. As such, an approach to implementation of TREC-based screening for SCID could include

strategies aimed at reducing this risk (for example, detailed communication in the obtaining of informed consent as described below).

As outlined in section 2.3.2, children with SCID should not receive live bacterial or viral vaccines due to the serious risk of morbidity and mortality associated with live vaccines in these children. While screening for ADA-SCID has been implemented by the NNBSP and other newborns may be identified early due to a known family history, in the absence of TREC-based screening for SCID, a child with SCID may receive a live vaccine, to their detriment, prior to diagnosis. Such cases may lead to distrust and hesitancy over the immunisation schedule for parents. This may result in a loss of confidence in the national childhood immunisation programme and a reduction in uptake in children for whom vaccination is safe and beneficial.

9.2.7 Perceptions and expectations of newborn screening

Regarding benefits and harms, the parental perception and expectation of screening is an important consideration. As will be further discussed under autonomy, in the absence of sufficient information and understanding, there may be misconceptions about the intent of screening, potential outcomes and impact of results.

While not specific to screening for SCID, the advocacy group Rare Diseases Ireland commissioned a survey in 2022 with the aim of exploring opinions of newborn screening; this study was conducted by the research agency iReach Insights with funding support from pharmaceutical groups (Kyowa Kirin and Novartis). Of 1,000 respondents, 56.6% were parents and 9.3% were members of Rare Diseases Ireland.[222] Of all respondents, 82% of agreed that they would like to be informed about a condition a child has even if the condition is not yet treatable, 76% agreed that there should be sufficient knowledge provided about a condition and how it develops over time, 73% agreed that the condition screened should be an important health problem, and 81% agreed that they would like to be informed about conditions even if they are not symptomatic until later in life.

Of note, a Dutch study on the parental perceptions of incidental findings detected through newborn screening for SCID, with a specific focus on ataxia telangiectasia, sought to investigate the perceived advantages and disadvantages associated with each of early detection and late detection of such a condition.[228] A quarter of the parents partaking in the study cited no advantage to the late detection of the condition, while others noted advantages including enjoyment of the asymptomatic years without worry or anxiety, the child not receiving a medical ‘label’ from birth, the opportunity to fully enjoy the maternity period (including the difficulty in processing difficult news in the period after giving birth) and the ability to have another child without any worry as being potentially advantageous. Disadvantages of

late detection of the condition included lack of knowledge of hereditary links (for family planning and cancer surveillance), potentially delayed access to supportive care, longer periods of uncertainty and worry, and not being mentally or financially prepared for the diagnosis. Parents were noted as valuing clarity and knowing what to expect in the case of early detection as opposed to potential uncertainty in late diagnosis.

9.3 Autonomy

9.3.1 Vulnerability of the target population

A core consideration of the ethical analysis domain is whether the target population of the proposed technology are considered to be vulnerable.[14] In the case of NBS screening, the target population is newborns who do not have capacity to consent to the programme and hence the consent process is deferred to that of the parents or caregivers. It should be considered that consent is sought from parents in the immediate days after birth which may be associated with emotional vulnerability in terms of stress and fatigue, potentially impacting on the parents' ability to truly provide informed and reasoned consent.[230, 237, 238]

9.3.2 Informed consent

In Ireland, the NNBSP is voluntary and parents are expected to make an informed choice regarding their child's participation in the programme, with an entitlement to opt out if they wish to do so.[239] The guidance states that parents should be provided with an information leaflet during the third trimester of pregnancy and again at the time of obtaining consent. Should a parent wish to opt out they are required to complete a form and be informed of the potential ramifications for the child's health in the event that they do have one of the conditions screened.[239] Should a parent change their mind, it is their responsibility to inform the public health nurse or GP of their desire to take up screening subsequently. The previously mentioned Irish survey of parental opinions of newborn screening indicated that 72% of parents felt they knew a lot or a little about the test while 28% only knew the test by name or had never heard of it.[222] In addition, 41% agreed they had received sufficient information about the test while the remaining 59% either disagreed or responded that they neither agreed nor disagreed. Lastly, 15% agreed that they considered whether or not the baby should have the test and 29% agreed that they took specific notice of the conditions screened for.

Informed consent in the context of NBS screening has been subject to ongoing debate within the literature.[238] It has been noted that the process of obtaining informed parental consent varies widely across and within jurisdictions.[237, 238] Internationally, there has been evidence to suggest that consent in the context of

NBS screening is less likely to be informed and that the screening is more likely to be perceived as routine or required.[230, 237, 238] The emphasis on informed consent is particularly challenging when considering the expansion of NBS screening programmes to include a larger number of diverse, and often complex, conditions.[230, 238] Meaningful parental understanding is a prerequisite for informed consent to NBS screening; however, the level of this understanding can be challenging to assess.[237, 238] Given the rarity and complexity of the conditions included in NBS programmes, alongside the intricacy of screening processes themselves, the provision of information to parents to fully meet the criteria of informed consent can be difficult to achieve.[230] UK data has suggested that while parents are generally happy with their decisions to partake in NBS screening, their knowledge about screening, and of the conditions screened and their potential impact, is typically low.[230] This is again compounded by the timing of the NBS test in the postnatal period, with the prenatal period frequently cited as key for information provision.[230, 237, 238]

The definition of the target of the screening process (as discussed in section 8.4) may also have implications for the informed consent process.[218] This definition varies internationally with some programmes considering the primary target to be SCID with non-SCID TCLs being secondary targets or incidental findings while other programmes may define the primary target as any significant TCL. The definition of the targets has implications for the informed consent process whereby it may be reasoned that, to be truly informed, parents need to be aware of the purpose, the process involved and each possible outcome of the screening test, and their subsequent impact, including the target condition (for example, SCID), incidental findings (for example, non-SCID TCLs), instances of false positives and false negatives.[240]

There may also be challenges to information provision in the context of two screening tests for SCID (that is, ADA-SCID by MS/MS and TREC-based screening for all SCID subtypes) within one overarching screening programme. Additionally, as highlighted in chapter 8, TREC-based screening raises another unique consideration when compared with other tests in the programme in that screening for SCID includes the analysis of DNA in the initial screening test (albeit, what is actually being screened is an absence of a DNA by-product).[226]

Considering a public audience, the general concepts associated with screening metrics, such as, sensitivity, specificity, false positives and false negatives, can be difficult to communicate. Nicholls et al.[238] speak to the challenges that exist in newborn screening in terms of the management of information, expectations, and parental understanding of the meaning of screening results. This has been referred to as the “burdensome nature of knowledge” or “communication burden”; a careful

balance is required to, on one side, not overstate the likelihood of positive results in the context of rare diseases while, on the other side, ensuring parents are well informed of the possibility. Furthermore, there is little consensus as to the best approaches to mitigate potential psychosocial harms associated with each side of this communication problem. There may be merit in a layering approach to the information provided for newborn screening; in this way, consent could be provided for the test overall while opportunities are afforded to the parents to ask further questions from a knowledgeable healthcare professional regarding specific conditions and their epidemiology should they desire.

In terms of NBS programmes generally, evidence has shown that adequate information provision improves and shapes parents' experiences of positive screening test results by reducing distress and confusion.[230, 237]

9.3.3 Social influence on autonomy

A 'one size fits all' approach to obtaining informed consent for NBS, is unlikely to be equitable, with programme expansion to include additional conditions adding to the complexity.[230] The assumption that the provision of information infers informed consent negates individual differences, social and cultural factors, and the ability of an individual to translate knowledge provided into informed decision-making.[230] Decision-making ability can be compromised by stressful environments in the context of recent childbirth, dependence on the medical system, trust or mistrust in medicine, and the challenges associated with new parenthood. Elements such as an information overload in the initial days after giving birth, fatigue, paternal anxiety and perceived expectations of partaking in a test seen to be routine can further play a role.[230] This is further compounded by the parents' baseline ability to read, write, retain and interpret information in terms of overall health literacy.[230]

Furthermore, parent and societal understanding of the distinction between screening and diagnostic testing is important to consider,[230] alongside an appreciation of the significance of timely follow-up testing and attendance at appointments.[238] Irish research has demonstrated that, for screening programmes in general, there is often some confusion surrounding the overall purpose of screening and whether or not screening programmes can diagnose a condition.[241] Specifically in the case of newborn screening, the previously mentioned Irish survey[222] highlighted that approximately half (56%) of respondents cited that they believed the primary reason for the heel prick test is to examine whether their baby is born with certain rare conditions; however, the survey did not further explore respondents' understanding of the differences between screening and diagnostic testing. Furthermore, 50% of individuals cited only wanting to be informed about a condition if it is certain that

their child has it; this opinion is noteworthy as it appears to be in contrast to the generally accepted principles of screening.

9.4 Respect for persons

The EUnetHTA Core Model[14] suggests that the impact of the technology on 'respect for persons' be considered in terms of effects on human dignity, moral, religious or cultural integrity, and the privacy of the participants. Considering these aspects, no ethical or social arguments were identified for the addition of TREC-based screening for SCID to the NNBSP.

9.5 Justice and equity

9.5.1 Healthcare resource use

Screening for SCID may be considered to be an equitable undertaking in that the NNBSP in Ireland is a voluntary programme which is offered to the parents and caregivers of all newborns. That is, there are no criteria by which an individual's right to participate is precluded. The current programme is associated with a high uptake rate with little evidence to suggest that uptake would decrease if screening for SCID was added.

As identified in chapters six and seven, there are uncertainties as to the cost effectiveness and budget impact of adding TREC-based screening for SCID to the NNBSP. Therefore, there are factors which relate to equitable use of resources at a population level when considering broader resource use and opportunity costs. The implementation of screening for SCID would likely represent an increased demand on diagnostic testing (such as flow cytometry and genetic tests), with further demand placed on clinical capacity in terms of appointments and waiting lists. Depending on the way in which screening for SCID is implemented and the mitigation strategies that are put in place, there is the potential for care to be displaced.

Given the immune deficiency associated with the condition, it is likely that a proportion of children identified through this form of screening would enter the system in time regardless of the presence of screening; however, their presentation in the context of screening would be accelerated. While the overall demand for resources will depend on elements such as the screening algorithm and cut-offs used and will likely only be borne out during the implementation phase, this factor should still be considered in decisions regarding implementation. In particular, the incidence of non-SCID TCLs detected through NBS programmes has been highlighted as a potential burden for these programmes.[63] These cases are likely to be a considerable driver of demand and capacity of the system. Furthermore,

uncertainty has been documented internationally regarding defined clinical pathways, and consensus on best practice for diagnosis, follow-up and management of such diagnoses detected through newborn screening for SCID.[50, 62-64]

9.5.2 Factors affecting access to the technology

As noted above, provision of consent for newborn screening is deferred to the parent or guardian of the child. Therefore, the perceptions of the parent directly influence the ability of the child to access screening. As previously discussed under the heading 'autonomy', such perceptions may be influenced by elements such as trust in healthcare, health literacy, prior experience, and individual beliefs.[230] Previous studies have highlighted that, albeit in small proportions, reasons for declining to participate in newborn screening for SCID have included insufficient provision of information (or misconceptions regarding such information), a low risk of the disease being present, not being interested in knowing if a child has the condition, or privacy concerns.[146]

The child is reliant on the parent for their access to each element of the care pathway. Given screening is associated with pathways of care rather than the isolated screening test, the factors outlined above will have an ongoing effect on care including the appreciation of the importance of follow-up testing and clinical examination, attendance at appointments, and access to treatment. There may also be social barriers in terms of access and ability to comply with therapies. HSCT (that is, the gold standard for the treatment of SCID) is currently provided in England through the HSE's Treatment Abroad Scheme. An assessment of the repatriation of this service for children with SCID, alongside other conditions, is ongoing at the time of writing. A decision to implement screening for SCID would result in earlier identification of the condition for many children with SCID, and, therefore, would result in more children and their families travelling to England for treatment at an earlier point of the infant's life.

9.5.3 Influence of home circumstances

In the context of SCID, the prevention of infection and adherence to IPC protocols is an integral element of management. It has been noted that home circumstances are an important clinical consideration as to whether a child with SCID is cared for at home or in the hospital setting for the interim period between diagnosis and definitive treatment. In the context of screening, the decision for a child to remain in hospital until treatment due to home circumstances will be made earlier in the child's life. Therefore, for some families this separation will be accelerated, albeit for the overall intended benefit of the child.

9.5.4 Detection of non-SCID TCLs

While the primary target of TREC-based screening may be SCID, the TREC cut-off, methodology, and diagnostic criteria used will determine the proportion of non-SCID TCLs that are identified by this from of screening.[50] It may be the case that only a certain proportion of a given population will be detected. For example, in those with 22q.11 Deletion Syndrome only those with significant immune impairment are likely to be detected, as described in Appendix 2.3. Additionally, not all serious TCLs will be identified using TREC-based screening; certain conditions (those which are associated with intact T-cell development beyond the point of TREC formation, such as ZAP-70 deficiency), can present with normal T-cell counts, even though immune function is severely impaired.[242] Therefore, while parents should be informed of the additional non-SCID TCLs that may be detected through screening, it should be clarified that, as the screening test was not designed to detect these non-SCID TCLs, it may not detect all such conditions.

9.6 Ethical consequences of the HTA

9.6.1 Availability of evidence

As highlighted throughout this report, the rarity of SCID results in limitations in the available evidence nationally and internationally to inform these types of assessments. Evidence relating to clinical outcomes of children with SCID is limited to observational studies (as opposed to, for example, randomised control trials) which frequently span multiple locations and decades. The design of more robust studies is unlikely to be considered ethical or feasible and hence it is unlikely that better evidence will ever become available. Perspectives on the future of research in NBS have discussed such challenges and advocated for patient registries and international collaboration to enable long-term follow-up of screening programmes and optimisation of strategies in the context of rare diseases.[243]

In terms of cost effectiveness, analyses are limited by the availability of reliable data to populate models in relation to screening for SCID. Hence, many estimates included are based on proxies, expert opinion, or are associated with much uncertainty. This presents a risk that decision-making may be relying on estimates which could under- or overstate the potential benefits or costs of screening. Much uncertainty was presented in terms of the number and impact of the non-SCID TCLs detected during screening for SCID. In particular, the heterogeneity of the potential causes of these conditions precluded inclusion of reliable treatment and outcome costs for this cohort. Furthermore, the use of quality-adjusted life years (QALYs) in newborn bloodspot screening research has been highlighted as challenging given the requirement for information regarding utility measures in newborns; such

information is notably difficult to obtain and interpret in the context of rare paediatric diseases.[199]

9.6.2 Timing of the HTA

A HTA is carried out at a point in time, and the timing of the assessment can have an important bearing on the outcome and perceived benefit. For many health interventions, the evidence base is dynamic as populations and interventions change. The NNBSP has recently implemented screening for one subtype of SCID, that is ADA-SCID, (May 2022) with limited time to assess the effect of this screening in the context of this HTA. Screening for ADA-SCID specifically is relatively novel with limited implementation internationally (at the time of writing, Tuscany, Catalonia, and Michigan are the only programmes the evaluation team are aware of). Evidence of the impact of TREC-based screening over and above ADA-SCID screening is not available.

The number of conditions included in a NBS programme is a further consideration to the timing of this HTA. Currently, the NNBSP screens for nine conditions; however, internationally there is ongoing advocacy for the expansion of NBS screening programmes. While not necessarily relevant to the current assessment, should the number of conditions under consideration increase substantially, there may be a compounding effect. The sequence and prioritisation in which NBS conditions are considered may become relevant from the perspective of finite budget availability and have implications for historical additions that were made to the programme. As such, there should be processes to ensure the ongoing validity of all conditions included in the NNBSP.

Lastly, this HTA is being completed at a time at which the potential repatriation (that is, movement of care) of HSCT services from the United Kingdom to Ireland for SCID cases (amongst other conditions) is undergoing current assessment by HIQA to inform decision making by the HSE. Repatriation of HSCT for these patients may have implications for access to treatment, follow-up care, and cost outcomes.

9.7 Discussion

The purpose of this chapter was to outline the potential ethical and social considerations associated with the addition of screening for SCID to the NNBSP in Ireland. The considerations outlined are framed in the context of relevant norms and values, with the aim of understanding the consequences of implementing or not implementing such a screening programme, as opposed to providing definitive guidance.

In terms of the benefit-harm balance, TREC-based screening for SCID requires consideration of multiple cohorts that may be detected including those with SCID, those with non-SCID TCLs and instances of false positives. The benefit-harm balance differs across these groups with clear benefit for children with SCID in terms of improved clinical outcomes, no benefit for those identified as false positives, and heterogeneity in terms of the potential non-SCID TCLs identified. Screening also has potential for both benefits and harms for the parents and family of the child involved, as well as potential impact on population engagement with and trust in national health programmes.

Screening for SCID involves a particularly vulnerable population in terms of newborns with consent by parents, potentially at time of stress and fatigue. The perceptions and expectations of screening programmes from the standpoint of the parents is an important consideration in terms of understanding the potential benefit – harm balance and in the ability to provide informed consent. Obtaining truly informed consent in the context of newborn screening can be challenging given the number, rarity and complexity of the conditions included in NBS programmes, alongside the intricacy of understanding screening processes themselves.[230] There is a need for a careful balance that does not overstate the potential for positive findings while ensuring the parent is informed of the potential outcomes and impact of screening.[238] In the context of screening for SCID specifically, the detection of non-SCID TCLs may complicate this process. The influence of socioeconomic factors and health literacy has further important bearing on how information is provided and translated into decision-making.

From the perspective of justice and equity, such parental factors may further impact the ability of the newborn to access screening, alongside having ongoing impact when considering the newborn's ability to access follow-up care and engagement with the clinical pathways outlined in chapter two in the case of positive screen results. Additionally, while the implementation of this form of screening may represent an equitable investment considering all newborns are offered screening, as documented in chapters seven and eight, there is a potential for displaced care and strain on the capacity of the system which may not be equitable at the population level. This is particularly relevant when considering the number of non-SCID TCLs that may be detected, and is further compounded by the uncertainties that exist in the estimates of cost-effectiveness and resource implications associated with screening for SCID as discussed in chapters six and seven.

There are limitations in the available evidence nationally and internationally to inform these types of assessments with many estimates based on proxies, expert opinion, or associated with much uncertainty, which poses a risk to overall decision-making. Furthermore, there are important considerations for the timing of the HTA

and the impact on overall findings in light of elements such as the recent, and relatively novel, addition of ADA-SCID screening to the NNBSP, the ongoing expansion of NBS programmes, and the current assessment of HSCT repatriation.

It should be noted that while the ethical and social considerations outlined are important and require due diligence in decision making, they are not necessarily unique to Ireland, nor to screening for SCID specifically, with previous international assessments highlighting similar areas for deliberation.[77, 82, 137] These findings have not precluded the implementation of the technology, but rather provided tangible factors that should be considered during decision-making and accounted for during subsequent implementation should a positive recommendation be made.

10. Discussion

10.1 Introduction

HTA is a multidisciplinary process that summarises information about the medical, social, economic, and ethical issues related to the use of a health technology.[14] A HTA is performed in a systematic, transparent, unbiased, and robust manner with the intention of supporting evidence-based decision-making regarding the optimal use of resources in healthcare services.

In September 2021, at the request of NSAC, HIQA agreed to undertake a HTA on the potential addition of TREC-based screening for SCID to the NNBSP. Of note, in the HTA, TREC-based screening for all SCID subtypes in the NNBSP was assessed in addition to the existing panel which includes screening for ADA-SCID (a SCID subtype) by tandem mass spectrometry.

The purpose of this discussion chapter is to summarise the key findings of the HTA, contextualise these findings relative to other assessments completed internationally, and present the strengths and limitations of the assessment overall.

10.2 Summary of key findings

The NSAC have produced a modified list of 20 criteria for appraising the viability, effectiveness and appropriateness of a screening programme (Appendix 2.1).[16] The main findings from this report are presented below in the context of these criteria.

The condition

As per the NSAC criteria, the condition should be an important health problem. This importance may be interpreted in different ways. As outlined in chapter 2, SCID typically presents asymptomatically at birth. However, it is judged a paediatric emergency which is almost uniformly fatal in the first year of life without appropriate treatment.[5-8] Therefore, the SCID population in Ireland represents a small, but clinically important group. The estimated birth prevalence of diagnosed SCID in Ireland is 1 in 39,760; for comparison the range of incidence reported for the conditions currently screened for in the NNBSP is 1 in 155,200 (maple syrup urine disease) to 1 in 2,300 (each of congenital hypothyroidism and cystic fibrosis). This estimated prevalence of SCID is relatively high compared with international estimates, particularly given that these estimates are largely based on the post-screening prevalence. Post-screening estimates may include cases that would previously have gone undiagnosed in the absence of screening (that is, children who may have died prior to being diagnosed with SCID). It is noted, however, that the

past approach of targeted screening for ADA-SCID, a SCID subtype accounting for approximately 50% of cases in Ireland, may have reduced the risk that cases of ADA-SCID went undiagnosed. The introduction of universal NBS screening for ADA-SCID in May 2022 will likely reduce this risk further. Nonetheless, the available international evidence suggests that the prevalence of diagnosed SCID may increase following the introduction of a TREC-based screening programme,[101, 106] providing an opportunity to initiate appropriate management and treatment in the form of HSCT, thereby reducing the risk of early mortality.

The screening method

NSAC criteria for the screening method states that the method should be simple, safe, precise, reliable, and validated. Currently, SCID is identified through ADA-SCID screening, family history or clinical presentation.

For the purposes of this assessment, it was assumed that a SCID screening programme comprising both ADA-SCID screening with tandem mass spectrometry and TREC quantification would have 100% sensitivity for the detection of all SCID subtypes, with the anticipation that the former would detect cases of delayed-onset ADA-SCID that may be not be detected by TREC-based screening. However, it is important to highlight that TREC-based screening is not specific to SCID. Other TCLs will also be identified with the number of non-SCID TCLs detected being highly dependent on the test methodology and TREC cut-offs established during the verification stage, alongside the epidemiology of the screened population. As outlined in chapter 4, a number of studies conducted in other contexts reported changes to the TREC cut-off used over the course of the study period, largely with the aim of reducing the number of false positives and non-SCID TCLs identified. If a decision is made to implement TREC-based screening for SCID, a balance will need to be achieved in the establishment of the screening method and TREC cut-off to maximise the identification of SCID cases, while minimising the risk of false positives and incidental findings of potentially unknown clinical significance.

The intervention

NSAC criteria regarding the intervention specify that there should be an effective intervention available for patients identified through screening, with evidence that this intervention when used in the pre-symptomatic stage leads to better outcomes for the screening cohort compared with usual care. Almost all studies identified in the systematic review of clinical effectiveness and safety (chapter 5) provided evidence to suggest that early diagnosis and or HSCT leads to improved survival outcomes compared with late diagnosis and or HSCT for children with SCID. As highlighted in chapter 3, data consistently suggest that the age at which children are

diagnosed, and, consequently, the age at which they undergo definitive treatment, is lower for those identified on the basis of screening or family history compared with those diagnosed clinically. The morbidity and mortality associated with SCID is significant; however, such factors appear largely reliant on the presence or absence of infections and complications prior to definitive treatment. Improved outcomes in infants diagnosed with SCID at an earlier age, and hence receiving HSCT earlier, may be explained by the lower risk of complications due to infection; such lower risk is likely in turn related to the opportunity to initiate infection prevention and control measures, prophylactic antibiotics, and immunoglobulin replacement therapy at an earlier time.

The screening programme

NSAC criteria specify that the opportunity cost of the screening programme should be economically balanced in relation to expenditure on medical care as a whole. The evidence relating to the cost effectiveness of TREC-based screening for SCID was based on a systematic review of economic evaluations (chapter 6).

The majority of the included studies identified that implementation of TREC-based relative to no screening would be a cost effective use of resources. However, none of the studies identified considered the introduction of TREC-based screening in the context of an existing population-based NBS screening programme that includes ADA-SCID screening (as adopted in Ireland in May 2022). In understanding the potential relevance of the results of the review, it is important to consider that, were screening for ADA-SCID in place, the incremental benefits relative to screening for ADA-SCID would be expected to be lower; this is because a proportion of the cases would already have been detected through such screening. However, the incremental costs would not be expected to be correspondingly lower. This would result in higher ICERs (that is, it would be less cost effective) than the estimates observed.

It is unlikely that the completion of a de novo cost-effectiveness analysis in the Irish context would provide additional insight given challenges associated with availability of data. Furthermore, in previous economic evaluations, the vast majority of cost-offsets associated with the earlier identification of clinically diagnosed SCID cases were associated with reduced HSCT costs. However, in Ireland, HSCT for SCID is provided in the UK through the Treatment Abroad Scheme at a fixed cost; this arrangement would limit the ability to realise any potential reduction in procedure costs associated with earlier access to HSCT. The potential repatriation of paediatric HSCT services is subject to an ongoing HTA by HIQA to inform decision-making by the HSE. Similarly, it should be acknowledged that estimates of epidemiology and clinical outcomes within this assessment may not be representative of changes

which would occur in the Irish setting, given many of these estimates come from international sources, with no universal screening for any form of SCID.

The absence of evidence for a comparator that includes ADA-SCID screening with tandem mass spectrometry is largely unsurprising; this method is a relatively novel screening approach with only screening programmes in Tuscany (Italy), Catalonia and Michigan (US) identified by the evaluation team as having introduced tandem mass spectrometry screening for ADA-SCID separate to TREC-based screening.[95, 212] Tuscany screens for ADA-SCID alongside numerous other conditions which can be screened using tandem mass spectrometry, while the decisions in Catalonia and Michigan were due to concerns for missing cases of delayed-onset ADA-SCID.[91, 95] If a decision is taken to implement TREC-based screening for SCID, it may be pragmatic to assess outcomes of this parallel testing as part of the ongoing quality assurance and performance management of the NNBSP; monitoring of such outcomes would assist in evaluation of the ongoing relevance of screening for ADA-SCID (in the context of TREC-based screening being in place).

While evidence of cost effectiveness informs decisions around the efficient use of healthcare resources, affordability is an important issue for the healthcare system. The total estimated budget impact to implement TREC-based screening (comprising laboratory verification and implementation and treatment of identified cases of SCID and non-SCID TCLs) was €3.66 million over five years. The budget impact was assessed in two parts. Part I, verification and implementation of TREC-based screening for SCID, was associated with an incremental budget impact of €3.0 million.

Uncertainty associated with the cost of the TREC test kit (consumables) was identified as a major contributor to uncertainty in the incremental budget impact for part I. Therefore, the incremental budget impact may be substantially reduced if a lower unit cost than assumed in the base case analysis can be agreed following the outcome of a formal tendering process. For example, in a scenario analysis completed with the cost of TREC test kits set at €3.12 (that is, the minimum expected cost based on the published literature) the incremental budget impact for part I of the analysis was reduced by approximately 20%. The incremental budget impact associated with the treatment of SCID and non-SCID TCLs (part II) was estimated at approximately €660,000. However, estimation of the clinical consequences of TREC-based screening for both SCID and non-SCID TCLs was challenging due to the small sample size and dearth of evidence directly applicable to the context of this assessment.

Additional NSAC criteria state that the screening programme needs to be acceptable to the population, that the benefit gained by populations and individuals from the

screening programme should outweigh the harms, and that the public should be informed of these harms and of their associated undesirable physical and psychological consequences. In terms of acceptability, the NNBSP has a notably high uptake rate with near population-wide coverage. While international literature would not suggest that the addition of TREC-based screening for SCID would lead to a reduction in uptake, this indicator should continue to be monitored through the NNBSP quality assurance processes to ensure trust in the programme is being maintained should a decision be made to implement. Chapter 9 addressed the potential ethical and social considerations associated with the addition of SCID to the NNBSP in Ireland. In terms of benefit-harm balance, this form of screening requires consideration of multiple groups that may be detected by the test, including those with SCID, those with non-SCID TCLs, and instances of false positives. The benefit-harm balance varies within and between these groups. As with prior changes to the NNBSP, an update of the programme material would be required.

With regards to autonomy, thought should be given to the obtaining of informed consent in the context of the number and complexity of the conditions screened, the intricacy of understanding screening processes themselves, and the unique scenario of the NNBSP screening for SCID using two separate tests. In terms of justice and equity, from a clinical perspective, a TREC-based screening programme for SCID would identify non-SCID TCLs. Identification of a relatively high number of non-SCID TCLs may present challenges for clinical capacity in terms of diagnosis and follow-up with the potential for displaced care and strain on the capacity of the system; however, this appears largely dependent on the findings of the verification stage. Additional ethical arguments presented in this chapter included factors such as perceptions of screening, limitations in the evidence available nationally and internationally to inform these types of assessments, and the timing of this HTA relative to elements such as data availability, the recent addition of ADA-SCID screening to the NNBSP, and the ongoing assessment of HSCT repatriation.

Implementation criteria

Introduction of TREC-based screening for SCID would require the use of new equipment and a testing method which is not currently available in the NNBSL. This would therefore require a capital investment, as well as a need for appropriate training and laboratory space. While use of such equipment would, in the first instance, be limited to TREC-based screening for SCID, there may be potential for downstream efficiencies should additional conditions utilising the same platform be added to the NNBSP. On a similar note, assays may have multiplex capability (that is, more than one condition can be screened for), which could result in efficiencies in the procurement of consumables.[225]

NSAC specify several criteria in relation to the implementation of a screening programme; these include the clinical management of the condition, the staffing and facilities for the various aspects of the programme and plans for monitoring of the programme, in addition to a number of criteria that have already been discussed. Organisational implications of the addition of TREC-based screening for SCID to the NNBSP were outlined in chapter 8. Key issues from the perspective of the laboratory would include the site of initial implementation, the availability of medical scientists, and potential operational efficiencies during the verification stage related to the addition of other NBS conditions that are tested using the same platform. Unlike many other larger countries, such as the UK, all testing for the NNBSP occurs in one centralised laboratory. As the testing is in one centre, this may assist with facilitating the necessary training and verification of the addition.

A decision to implement SCID screening at the NNBSL in CHI Temple Street, which would require reconfiguration of the existing laboratories, or to defer implementation until the laboratories at the new children's hospital are operational, would be highly dependent on a number of time-sensitive factors. The potential lag time between decision-making and implementation, approval of funding, tendering and procurement, and opening of the new children's hospital, will influence the feasibility of implementing TREC-based screening at CHI Temple Street from a system's perspective. Such decisions around practical feasibility will need to be considered also in the context of the level of acceptable risk associated with deferring implementation (that is, the potential for missed cases). It is noted that the current staffing issues in medical laboratories may present challenges for recruitment.[217] Also, potential challenges associated with recruitment and retention could impact timely verification and implementation (and therefore the feasibility of implementation at CHI Temple Street) alongside existing workload.

For conditions that meet the evidence bar for inclusion in the NNBSP, there may be efficiencies for the programme if implementation is deferred until a number of changes to the programme can be made at the one time rather than proceeding with sequential additions (that is, as soon as a positive recommendation is made). From the laboratory perspective, these efficiencies relate to the verification processes, should the conditions require the same screening technology (that is, the verification can be run simultaneously on the same platform). More broadly, there may be additional efficiencies relating to training requirements and programme adjustments. These should also be borne in mind in the context of the timing of the upcoming move of the NNBSL to the new children's hospital. However, as noted, these potential efficiencies for the programme would need to be weighed against the individual clinical benefit for children that would be identified through screening.

10.3 Findings relative to international assessments

Several national and regional health organisations have previously completed assessments for the addition of TREC-based screening to an NBS programme, including two from provinces in Canada (Quebec[77] and Alberta[192]), France,[82] Spain,[195, 244] and the UK.[62] All of the identified reports explored adding TREC-based screening for SCID to an established NBS programme. Overall, the majority of assessments reported similar findings to this report, with all except one recommending the addition of screening for SCID, and each highlighting important considerations for implementation locally. The key findings and considerations from each of the reports are described in below.

The report from France noted that although there is evidence in favour of screening for SCID at birth, numerous uncertainties exist.[82] The assessment was planned to be based on the results of a pilot study conducted in the country; however, it was not possible to conclude on clinical and economic impact due to the small number of infants identified with SCID during the pilot, and therefore the assessment was based on data from a registry, and analysis of literature and experience from other countries.

Similar to this current review, the report highlighted that screening would allow for an expedited diagnosis and appropriate management of the infant, and that TREC-based screening was considered to be feasible. Furthermore, it was noted that, although there were insufficient data to perform an economic assessment specifically for France, the authors considered that the model from the UK could be considered transferable to the French context; however, there were uncertainties noted such as the impact of false positives and non-SCID TCLs on the cost effectiveness. Factors highlighted included anxiety and disruption of the parent-child relationship, as well as the difficulty in assessing the benefit of screening for the non-targeted diseases which are identified in the process.

Due to these uncertainties, the committee recommended the conditional addition of screening for SCID, contingent on a five-year evaluation, with regular interim evaluations throughout this time. It was also emphasised that screening should only be introduced conditional on the capability of the healthcare system to be able to provide HSCT within two months of birth, which would require strict compliance with the timelines identified for each step of the screening process.

The reports from Spain on the addition of TREC-based screening for SCID concluded that the evidence on effectiveness of screening was of low methodological quality and based primarily on observational studies and limited pilot programmes.[195, 244] However, the authors did conclude that screening for SCID would be expected to

achieve clinical benefit, noting that there is an effective treatment which is more effective if performed before an infant with SCID becomes symptomatic. The authors also concluded that the cost effectiveness of introducing screening for SCID was dependent on the cost of the test and the incidence of the disease, and recommended that the cost effectiveness and impact be evaluated in the medium and long term if screening were to be introduced.

Contrary to the other countries identified, based on a 2017 review, the UK National Screening Committee (NSC) conditionally recommended against screening for SCID.[62] Due to the uncertainty in the rate of false positives, the proportion of infants identified through a family history of SCID, and the ability for the laboratories to handle the increase in capacity should screening for SCID be implemented, as well as a lack of clarity on pathways for infants diagnosed with non-SCID TCLs, the NSC requested that a pilot programme be implemented and evaluated before a final recommendation is made. At the time of writing, this pilot is ongoing and is expected to last for two years. In considering the applicability of a pilot approach in the Irish context, it is important to note that given the small birth cohort in the context of screening for a rare disease, pilot studies are unlikely to be feasible or useful for gathering reliable estimates.

The Canadian HTA report from Quebec explored adding SCID to the province's established NBS programme.[77] Similar to the current HTA, the assessment highlighted the need for care regarding the optimal TREC cut-offs, given implications for the proportion of non-SCID TCLs identified as well as the need for a specific algorithm for premature infants or those in NICU. Modifications to the vaccination programme were recommended in addition to the requirement for guidance on the communication of incidental findings, particularly for incurable conditions such as Ataxia Telangiectasia. Additionally, in order to reduce potential public reservations about molecular testing, dissemination of information about the test and the condition were stated as important.

Following a deliberative process by an expert committee, it was recommended that screening for SCID should be added to the NBS programme in Quebec. The other Canadian report identified, from the province of Alberta (Canada),[192] explored the potential addition of screening for SCID independently, or as a combination with up to seven conditions to the NBS programme. This report may not be directly comparable to this HTA which focuses solely on the addition of TREC-based screening for SCID to the NNBSP in Ireland.

10.4 Strengths and limitations

The findings of this assessment should be considered in light of its overall strengths and limitations. Firstly, a robust approach to the assessment was employed with publication of a protocol for the HTA,[180] and the establishment of an Expert Advisory Group (EAG) comprising a broad range of both national and international key stakeholders to support the assessment.

The HTA was conducted in accordance with national and international HTA guidelines. Additionally, preliminary work was completed to map the NSAC criteria for appraisal of screening programmes[245] to the domains of HTA to ensure the evidence presented aligned with criteria for decision-making.[180] Information included within the HTA was obtained from best available evidence, which included the use of systematic review methodology to identify and summarise the available literature for each domain of relevance, while adhering to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria. However, important limitations exist in relation to the currently available evidence to support this HTA which must be interpreted in in the context of the overall findings.

SCID is a rare disease and, as such, there are challenges in research relating to this condition. While national sources were used wherever possible, the majority of evidence identified for this HTA comprised international evidence from various countries and sources, which may limit the overall applicability. Historically, estimates of the incidence of SCID in a population have been considered to be underestimated, and the incidence is noted to vary widely across geographic locations and within certain populations.[25]

Using international evidence to inform estimates of the incidence of SCID in Ireland may under- or overestimate the full extent of the disease, making estimation of changes in clinical and economic consequences arising from the addition of TREC-based screening to the NNBSP challenging. Similarly, given the nature and rarity of SCID, the evidence within this HTA for the clinical impact of early diagnosis and or HSCT in patients diagnosed with SCID was primarily obtained from observational studies undertaken in other countries across multiple decades; this raises concerns regarding the applicability to the context of this assessment.

It should be noted that despite these limitations, the body of evidence was relatively consistent in its findings, that is, that earlier diagnosis and or HSCT results in improved clinical outcomes and survival for children with SCID. An additional challenge is that the estimates of test accuracy obtained from chapter 4 were obtained from studies with heterogeneous screening algorithms, methodologies, and TREC cut-offs in place. Such estimates would only be borne out reliably at the

verification and implementation phase in the local context following the establishment of population norms.

The BIA was undertaken in two parts reflecting the different phases of the screening programme and data available to support input parameters. As noted in section 10.2, there is considerable uncertainty regarding the unit cost of the TREC test kit, which comprises a substantial proportion of the overall incremental budget. Nevertheless, the cost estimate used in this BIA represents the best available evidence at the time of assessment, and is consistent with the international literature. There is also limited availability of reliable data to support input parameters for part II of the BIA. Uncertainty regarding key epidemiological parameters, including estimates of the undiagnosed SCID population in Ireland and the number of non-SCID TCLs of unknown clinical significance that may be detected, presents challenges for estimation of treatment costs following the introduction of TREC-based screening for SCID. In addition, given the clinical heterogeneity associated with non-SCID TCLs, reliable estimation of costs associated with the management of this population is not possible. Assumptions regarding the epidemiological and clinical implications of TREC-based screening were therefore guided by expert opinion and the international literature, and where they were subject to considerable uncertainty, these were extensively tested in sensitivity and scenario analyses to quantify the impact of parameter uncertainty. Nonetheless, these limitations present a risk that decision-making in the Irish context may be relying on estimates which could under- or overstate the potential benefits or costs of screening in Ireland. However, it is important to note that given the rarity of the condition, high quality evidence to support decision-making is unlikely to be generated.

Decision-making regarding the introduction of a TREC-based screening programme should be made with cognisance to the limitations of the underlying data. In this context, and in line with NSAC criteria, there should be a plan for managing and monitoring of the programme, should a decision be made to implement TREC-based screening for SCID, against an agreed set of quality assurance standards.

Chapter nine outlined the potential for reduced trust in childhood immunisation programmes arising from a lack of implementation of screening for SCID; this may occur in the event that children with SCID were to receive live vaccines to their detriment prior to being diagnosed. Should trust be undermined, there would likely be additional indirect costs associated with this. These may include both adverse health impacts at an individual and population level, due to failure to access beneficial vaccination, and costs associated with resource use from a programme perspective, including any initiatives and communication efforts required to restore trust. Studies identified in the systematic review of cost effectiveness (chapter six)

did not include such costs nor were they included as part of the budget impact analysis in chapter seven; however, the potential for these costs may be a factor for consideration.

10.5 Conclusion

SCID is a rare, but serious condition which is almost uniformly fatal in the first year of life without appropriate treatment. National and international evidence consistently suggests that earlier identification, and earlier treatment, for SCID results in better clinical outcomes for the child in terms of reduced morbidity and mortality. Early identification of infants with SCID through screening also facilitates the avoidance of live vaccines, which can be detrimental to the health of children with SCID.

The addition of TREC-based screening for SCID will further enable the earlier detection of infants that will otherwise present clinically, as well as the potential detection of children that would otherwise experience early mortality prior to a diagnosis being made. While considered sensitive, TREC-based screening for SCID is not specific to SCID. Other TCLs will also be identified, and it is likely that the incidence of these non-SCID TCLs detected through screening would be higher than that of SCID. The testing method and screening algorithm will need to be developed and verified to ensure optimal sensitivity and specificity is achieved.

The incremental budget impact of the addition of TREC-based screening to the NNBSP was estimated at €3.66 million over five years. This estimate was driven largely by the cost of the TREC test kit, the new equipment and laboratory staff necessary to implement the testing, and the potential for an increase in post-screening prevalence.

Given the scheduled move of the NNBSL to the new children's hospital, the timing of verification and implementation would have important implications as there are already extensive ongoing project management and resource requirements. Implementation prior to the move would necessitate structural reconfiguration of the existing laboratory as well as additional workload for the laboratory at a time when there is finite capacity for same.

If TREC-based screening for SCID is implemented, the quality assurance programme of the NNBSP should consider the monitoring and evaluation of outcomes against agreed standards to confirm the ongoing relevance of also screening for ADA-SCID.

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Appendices

Appendix 2.1 NSAC criteria for appraising the viability, effectiveness and appropriateness of a screening programme

In 1968, a report on screening by Wilson and Jungner, which was commissioned by the WHO, outlined ten principles which should be considered in decision-making relating to screening.[221] The authors explained that the term 'principles' was used for ease of description,[221] although the ten principles have been commonly termed 'criteria' in the subsequent literature.[246] Referred to generally as the 'Wilson and Jungner criteria', they have formed the cornerstone of screening decisions internationally. However, advances in disease understanding, technology, and a growing appreciation of the diverse complexities associated with screening have since triggered modifications to, and variations of, the original criteria.[246, 247]

While the original aim of the Wilson and Jungner criteria was to stimulate discussion and exchange of viewpoints in relation to screening, as opposed to providing a rigid checklist,[247] there has been a growing appreciation that even when the 10 criteria are satisfied, there may still be additional logistical, social or ethical reasons that contest screening.[246, 247] A 2018 systematic review of principles for population-based screening decisions, and a subsequent Delphi consensus process, presented a consolidated list of international criteria that are in use.[247] The authors concluded that, while the original Wilson and Jungner criteria have stood the test of time and remain core elements of screening policy internationally, there has been a growth in emphasis placed on programme or system considerations, including those which relate to the acceptability and ethics associated with screening programmes, and the balancing of benefits and harms.

As presented below, in line with the original Wilson and Jungner criteria described by the WHO, NSAC adopted a modified list of 20 criteria for appraising the viability, effectiveness and appropriateness of a screening programme.

- **The Condition**

  1. The condition should be an important health problem. The epidemiology, incidence, prevalence and natural history of the condition should be understood, including development from latent to declared disease and/or there should be robust evidence about the association between the risk or disease marker and serious or treatable disease.

  2. All the cost-effective primary prevention interventions should have been implemented as far as practicable.

3. If the carriers of a mutation are identified as a result of screening, the natural history of people with this status should be understood. The psychological implications should be considered, and the necessary psychological supports should be in place.

- **The Screening Method**

4. The screening method should be, as far as is practicable, be: simple, safe, precise, reliable, and validated

5. The distribution of screening values in the target population should be assessed and suitable cut-off levels/measurements defined and agreed by the applicant.

6. The screening process should be acceptable to the target population.

7. There should be an agreed policy on the further diagnostic investigation of individuals with a positive screening result and on the choices available to those individuals.

8. If screening is for a particular mutation(s) or set of genetic variants the method for their selection should be kept under review.

- **The Intervention**

9. There should be an effective intervention for patients identified through screening, with evidence that intervention at a pre-symptomatic phase leads to better outcomes for the screened individual compared with usual care.

10. There should be agreed evidence-based policies covering which individuals should be offered interventions and the appropriate intervention to be offered.

- **The Screening Programme**

11. Ideally there should be evidence from high quality randomised controlled trials that the screening programme is effective in reducing mortality or morbidity. Where screening is aimed solely at providing information to allow the person being screened to make an informed choice, there must be evidence from high quality trials that the test accurately measures risk. The information that is provided about the test and its outcome must be of value and readily understood by the individual being screened.

12. There should be evidence that the complete screening programme (test, diagnostic procedures, treatment/ intervention) is acceptable and can be implemented.

13. The benefit gained by populations and individuals from the screening programme should outweigh the harms. The public should be informed of these harms and of their associated undesirable physical and psychological consequences.

14. The opportunity cost of the screening programme (including testing, diagnosis and treatment, administration, training and quality assurance) should be economically balanced in relation to expenditure on medical care as a whole (value for money). Assessment against these criteria should have regard to evidence from cost benefit and/or cost effectiveness analyses and have regard to the effective use of available resource.

- **Implementation Criteria**

15. Clinical management of the condition and patient outcomes should be in place before a screening programme is initiated.

16. Adequate staffing and facilities for testing, diagnosis, treatment and programme management should be available prior to the commencement of the screening programme.

17. All other options for managing the condition should have been considered (such as improving treatment or providing other services), to ensure that no more cost-effective intervention could be introduced, or current interventions increased within the resources available.

18. There should be a plan for managing and monitoring the screening programme against an agreed set of quality assurance standards. This should include monitoring performance against different subgroupings in the population.

19. The potential benefits and harms of screening, investigation, preventative intervention or treatment, should be made available and explained to the eligible participants to assist them in making an informed choice. There should be a clear system of communication incorporated into each screening programme to ensure patients are kept aware of any developments in their case.

20. Decisions about commencing, expanding or ceasing a programme should be based on scientifically validated evidence.

Appendix 2.2 Governance and organisation of NNBSP in Ireland

The NNBSP is integrated within overall child health services in Ireland (that is, it is not part of the National Screening Service, which oversees breast cancer, cervical cancer, bowel cancer, and diabetic retinopathy screening programmes). Depending on the location of sample collection (that is, hospital or community setting), detailed pathways exist with various agencies responsible for individual elements, such as, sample collection, transport, analysis, recording, and onward referral.[18] Overall responsibility for the NNBSP in Ireland is with the HSE and the NNBSP Governance group, while the Director of the National Newborn Bloodspot Screening Laboratory (NNBSL) is responsible for the day-to-day coordination and management of the programme.[18]

Appendix 2.3 Vignette: 22q.11.2 Deletion Syndrome

As outlined in chapters two and four, depending on the screening algorithm and cut-off values used, newborn screening for SCID may result in the identification of a range of other non-SCID TCLs, including congenital syndromes, secondary causes of TCLs, and TCLs which are idiopathic in nature. Given the differential diagnoses that may be identified by this form of screening, it is important that the infrastructure for diagnosis, follow-up and management for such diagnoses is considered within decision-making.[50, 62] One specific syndrome, 22q.11.2 Deletion Syndrome (DS), also known as DiGeorge syndrome, was frequently noted as a differential diagnosis in the studies outlined in chapter four. Given the number of potential congenital syndromes that may be detected through newborn screening for SCID, it is beyond the scope of this assessment to examine each in detail; however, for illustrative purposes a vignette focusing on 22q.11.2 DS is presented below.

22q.11.2 DS is a genetic condition caused by microdeletions along chromosome 22, with diagnosis occurring through genetic testing.[248-250] The prevalence of the condition has been estimated as ranging from 1 in 2,148 to 1 in 6,000 live births; however, given the heterogeneity in terms of clinical severity, attaining accurate prevalence estimates is noted to be challenging.[250-252] In a retrospective review of 1,421 patients with the condition diagnosed between 1992 and 2018 at a centre in Philadelphia, the median age of diagnosis was 360 days.[253] Identification occurred significantly earlier in patients with cardiac signs (median age 2.6 months) compared to those without (median age 3.1 years).[253]

The diversity in the microdeletions that may be present results in a notably heterogeneous clinical presentation, with a variety of systems potentially impacted, including cardiovascular, immune, endocrine, genitourinary, gastrointestinal, musculoskeletal, and central nervous.[249] This heterogeneity leads to a range of possible symptoms, which tend to vary across the life span,[250] including, but not limited to:[249, 250] congenital heart disease, palatal abnormalities, dysphagia, laryngo-tracheoesophageal abnormalities, structural gastrointestinal anomalies, hernias, immunodeficiency, autoimmune disorders, ophthalmologic and craniofacial features, hearing impairment, hypotonia, microcephaly, seizures, developmental delay, intellectual disability and psychiatric disorders. Given the heterogeneity of the clinical pattern of 22q.11.2 DS, treatment is dependent on symptom development and may include a wide range of clinical specialties.[249] Management guidelines for 22q.11.2 DS, for both children and adults, have been outlined by The International 22q11.2 Deletion Syndrome Consortium.[254, 255] A dedicated 22q.11.2 DS clinic for patients with this condition has been established at CHI Crumlin.[256]

The presence and severity of symptoms vary widely between patients; however, of relevance to the current assessment, an element of immune dysfunction is estimated to be present in approximately 75% of childhood cases.[249, 250, 253] The pathophysiology associated with immunodeficiency in 22q.11.2 DS typically stems from thymic hypoplasia and subsequent impaired T-cell function.[249] However, it is challenging to estimate how many cases present with clinically significant immunodeficiency.[248]

A retrospective review of patients with 22q.11.2 DS at a centre in Philadelphia illustrated that following newborn screening, 11 patients had an abnormal screen result with SCID subsequently excluded through flow cytometry.[251] Five of these 11 patients had major congenital anomalies resulting in a diagnosis of 22q11.2DS being made prior to or concurrently with the timing of the abnormal screening result. The remaining six patients were identified through an abnormal screening result prompting evaluation and subsequent diagnosis.[251] The denominator of the total number of patients who had undergone screening was unclear and hence estimates cannot be provided for the proportion of 22q.11.2 DS likely to be identified through a newborn screening programme.

A second study from Ontario prospectively analysed, using multiplex qPCR assays, 30,074 DBS samples from a newborn screening programme in order to test for 22q11.2 deletions. The study identified 14 children with 22q.11.2 DS, with 13 being full term births. As part of the existing newborn screening programme, Ontario screens for SCID using TREC-based screening. Of these full term births identified with 22q11.2 deletions, six (46.2%) also met the initial screen positive cut-off value for SCID of 100 or fewer TREC copies per 3µL; this compared with 81 (0.3%) of all other NBS samples.[252] In Ontario, samples with an initial positive screen proceed to a second TREC assay, run in duplicate, with a TREC cut-off of 75 copies per 3µL; following the second TREC test, one child in the 22q11.2 DS group was below the screen-positive cut off.

In summary, an uncertain proportion of children with 22q.11.2 DS may be detected through newborn screening for SCID. However, only those with significant TCL will be detected in this manner.[248] Early identification of these children may have clinical merit in terms of implementing infection prevention measures, the avoidance of live vaccines, and the initiation of appropriate treatment.[248, 249]

Appendix 2.4 Status of newborn screening for SCID internationally

Country Region Source	Status of newborn screening for SCID	Total number of conditions screened for
Australia 1. HIQA. *Review of NBS Policy-making processes*, July 2021 2. Australian Government - Department of Health, *Newborn bloodspot screening,* https://www.health.gov.au/health-topics/pregnancy-birth-and-baby/newborn-bloodspot-screening, Updated: December 2021 3. Australian Government - Department of Health and Aged Care, *How we decide what conditions to test for,* https://www.health.gov.au/initiatives-and-programs/newborn-bloodspot-screening/how-we-decide-what-conditions-to-test-for#nominated-conditions, Updated: July 2022	Progressed to full review stage following initial review. Recommendations from detailed review currently under consideration. Under pilot in New South Wales. Queensland and Victoria have committed to implementation in 2023.	25
Austria Medical University of Vienna. *Neonatal screening: programme successfully expanded,* https://www.meduniwien.ac.at/web/en/about-us/news/2022/news-in-june-2022/neugeborenen-screening-erweiterung-erfolgreich-umgesetzt/, Updated: June 2022	Under evaluation as of 2021	26
Belgium Belgian Health Care Knowledge Centre. *Multi Criteria Decision Analysis to Select Priority Diseases for Newborn Blood Screening*, https://kce.fgov.be/sites/default/files/atoms/files/KCE_267_Newborn_blood_screening.pdf Updated April 2016	Not currently screened for	15

Bulgaria Loeber et al. *Neonatal Screening in Europe Revisited: An ISNS Perspective on the Current State and Developments Since 2010,* March 2021	Not currently screened for	3
Canada*		
Alberta HIQA. *Review of NBS Policy-making processes*, July 2021	Full implementation since 2019	21
British Columbia Perinatal Services British Columbia. http://www.perinatalservicesbc.ca/our-services/screening-programs/newborn-screening-program/disorders-screened Updated: unclear	Not currently screened for	24
Manitoba 1. Manitoba Health and Seniors Care. *Annual Report 2020/2021*, https://www.gov.mb.ca/health/annualreports/docs/2021.pdf 2. Manitoba Health and Seniors Care. *Newborn Screening in Manitoba,* https://www.gov.mb.ca/health/publichealth/cpl/baby.html Updated: unclear 3. Thompson JR et al. *Development of a Population-Based Newborn Screening Method for Severe Combined Immunodeficiency in Manitoba, Canada*. 2018	Under implementation since 2021(1)	40+(2)
New Brunswick Nova Scotia Prince Edward Island Maritime Newborn Screening Programme, IWK Health Centre. *Newborn Screening Manual,* https://www.iwk.nshealth.ca/sites/default/files/mnsp/hcp/newborn-screening-manual.pdf?m=112018 Updated: Sept 2018	Full implementation since 2016	22+

Newfoundland and Labrador Canadian Organization for Rare Disorders. *NBS in Canada Status Report*, https://www.raredisorders.ca/content/uploads/Canada-NBS-status-updated-Sept.-3-2015.pdf Updated: Sept 2015	Not currently screened for	7
Ontario 1. HIQA. *Review of NBS Policy-making processes*, July 2021 2. Newborn Screening Ontario. *Annual Report to the Newborn Screening Ontario Advisory Council – Public Version.* https://www.newbornscreening.on.ca/sites/default/files/2019_nso_annual_report_final_public.pdf Updated: 2019	Full implementation[1, 2] since 2013	25+[1, 2]
Quebec INESS *Dépistage du syndrome d'immunodéficience combinée sévère* https://www.inesss.qc.ca/fileadmin/doc/INESSS/Rapports/Depistage/INESSS_SCID_Avis.pdf	Evaluation completed in 2022 with positive recommendation	11
Saskatchewan Saskatchewan Government, *Saskatchewan Expanding Newborn Screening Program, https://www.saskatchewan.ca/government/news-and-media/2022/february/23/saskatchewan-expanding-newborn-screening-program*	Recommended for screening in 2022	30+
Croatia Klinicki bolnicki centar Zagreb. *Public information on neonatal screening**, https://www.kbc-zagreb.hr/informacije-javnosti-o-novorodjenackom-probiru.aspx Updated: Dec 2017	Not currently screened for	8
Cyprus	Not currently screened for	2

Center for Preventive Paediatrics. *Neonatal Screening Program*, https://www.cpp.org.cy/en/page/programma-proliptikou-elegxou-neognon Updated: unclear		
Czech Republic National Coordination Centre for Newborn Screening. *Neonatal screening in the Czech Republic,* https://www.novorozeneckyscreening.cz/en/for-health-care-proessionals Updated: unclear	Not currently screened for	18
Denmark 1. HIQA. *Review of NBS Policy-making processes*, July 2021 2. Statens Serum Institut (Denmark). *Diseases screened for*, https://nyfoedte.ssi.dk/medfoedte-sygdomme/sygdomme-der-screenes-for Updated: Oct 2021	Full implementation[1] since 2020[2]	18[1, 2]
Estonia Tartu University Hospital Joint Laboratory Center for Clinical Genetics. *Newborn Screening**, https://www.kliinikum.ee/geneetikakeskus/vastsuendinute-skriining Updated: 2021	Not currently screened for	21
Finland 1. Southwest Finland Hospital District. *Diseases screened**, https://www.vsshp.fi/fi/saske/seulottavat-sairaudet/Sivut/default.aspx Updated: June 2021 2. Palveluvalikoima. *Screening for SCID in a neonatal blood spot sample,* https://palveluvalikoima.fi/documents/1237350/38358696/Suositus_SCID+seulonta.pdf/29d70e3c-c17a-8b6a-acff-	Recommended for screening in 2020	20+[1, 2]

dd1180f2185a/Suositus_SCID+seulonta.pdf?t=1602084320287 Updated Sept 2020 3. Ministry of Social Affairs and Health. *Screenings in Finland 2014 The present state of health care screenings and future prospects*, https://julkaisut.valtioneuvosto.fi/bitstream/handle/10024/74717/STM_Screenings_i_finland_2014_Enkku_B5_nettiin.pdf Updated: 2014		
France Haute Autorité de Santé. *Évaluation a priori de l'extension du dépistage néonatal au Déficit Immunitaire Combiné Sévère par la technique de quantification des TRECs en population générale en France,* https://www.has-sante.fr/upload/docs/application/pdf/2022-01/argumentaire_evaluation_a_priori_de_lextension_du_depistage_neonatal_au_deficit_immunitaire_combine_severe_par_la_technique_.pdf February 2021	HTA completed in 2022 with conditional recommendation following pilot programme	6
Germany 1. HIQA. *Review of NBS Policy-making processes*, July 2021 2. Gemeinsamen Bundesausschusses. *Richtlinie des Gemeinsamen Bundesausschusses über die Früherkennung von Krankheiten bei Kindern (Kinder-Richtlinie)*, https://www.g-ba.de/downloads/62-492-2432/367b0ceb63c35f645f35425697ac6cf4/Kinder-RL_2020-12-17_iK-2021-04-01.pdf Updated: Dec 2020	Full implementation[1, 2] since 2019[2]	19[1]
Greece Loeber et al. *Neonatal Screening in Europe Revisited: An ISNS Perspective on the Current State and Developments Since 2010,* March 2021	Not currently screened for	4
Hungary Loeber et al. *Neonatal Screening in Europe Revisited: An ISNS Perspective on the Current State and Developments Since 2010,* March 2021	Not currently screened for	27

Iceland Landspítali University Hospital. *Neonatal screening,* https://www.landspitali.is/sjuklingar-adstandendur/deildir-og-thjonusta/onaemisfraedideild/, Updated: unclear	Full implementation since 2017	28
Italy 1. HIQA. *Review of NBS Policy-making processes*, July 2021 2. Malvagia et al. *The successful inclusion of ADA SCID in Tuscany expanded newborn screening program*, May 2021	Regional implementation and pilot	40
Latvia Loeber et al. *Neonatal Screening in Europe Revisited: An ISNS Perspective on the Current State and Developments Since 2010,* March 2021	Not currently screened for	6
Lithuania Loeber et al. *Neonatal Screening in Europe Revisited: An ISNS Perspective on the Current State and Developments Since 2010,* March 2021	Not currently screened for	4
Luxemburg Luxemburg Ministry of Health, *Screening for 5 genetic diseases (neonatal screening),* https://sante.public.lu/fr/prevention/petite-enfance/tests-depistage/5-maladies-genetiques/index.html Updated: October 2019	Not currently screened for	5
Malta Loeber et al. *Neonatal Screening in Europe Revisited: An ISNS Perspective on the Current State and Developments Since 2010*, March 2021	Not currently screened for	3

The Netherlands 1. National Institute for Health and Environment Ministry of Health, Welfare and Sport. *Heel prick,* https://www.pns.nl/hielprik Updated: unclear 2. Loeber et al. *Neonatal Screening in Europe Revisited: An ISNS Perspective on the Current State and Developments Since 2010*, March 2021 3. Blom et al. *Introducing Newborn Screening for Severe Combined Immunodeficiency (SCID) in the Dutch Neonatal Screening Program*, December 2018	Full implementation since January 2021[2]	24
New Zealand 1. HIQA. *Review of NBS Policy-making processes*, July 2021 2. National Screening Unit (New Zealand), *Screening for severe combined immune deficiency*, https://www.nsu.govt.nz/health-professionals/newborn-metabolic-screening-programme/screening-severe-combined-immune, Updated: May 2018	Full implementation since 2017	23
Norway 1. Oslo University Hospital, *Newborn screening,* https://oslo-universitetssykehus.no/avdelinger/barne-og-ungdomsklinikken/nyfodtscreeningen/nyfodtscreening, Updated: August 2021 2. Nye Metoder, *Nasjonal behandlingstjeneste for screening av nyfødte*, https://nyemetoder.no/metoder/nasjonal-behandlingstjeneste-for-screening-av-nyfodte, Updated: unclear	Full implementation since 2018[2]	26
Poland 1. Loeber et al. *Neonatal Screening in Europe Revisited: An ISNS Perspective on the Current State and Developments Since 2010*, March 2021	Pilot	29

2. Giżewska et al. *Newborn Screening for SCID and Other Severe Primary Immunodeficiency in the Polish-German Transborder Area: Experience From the First 14 Months of Collaboration*, October 2020		
Portugal Loeber et al. *Neonatal Screening in Europe Revisited: An ISNS Perspective on the Current State and Developments Since 2010*, March 2021	Not currently screened for	24
Romania Loeber et al. *Neonatal Screening in Europe Revisited: An ISNS Perspective on the Current State and Developments Since 2010*, March 2021	Not currently screened for	4
Slovakia Loeber et al. *Neonatal Screening in Europe Revisited: An ISNS Perspective on the Current State and Developments Since 2010,* March 2021	Pilot	27
Slovenia Loeber et al. *Neonatal Screening in Europe Revisited: An ISNS Perspective on the Current State and Developments Since 2010*, March 2021	Not currently screened for	20
Spain 1. HIQA. *Review of NBS Policy-making processes*, July 2021 2. Argudo-Ramírez et al. *Newborn Screening for SCID: Experience in Spain (Catalonia),* 2021	Full implementation in Catalonia.	7 core conditions, however the number varies between regions
Sweden	Full implementation since August 2019	25

1. Socialstyrelsen. *Svår kombinerad immunbrist,* https://www.socialstyrelsen.se/stod-i-arbetet/sallsynta-halsotillstand/svar-kombinerad-immunbrist/ Updated: December 2020 2. Göngrich et al. *First Year of TREC-Based National SCID Screening in Sweden*, 2021		
Switzerland Children's Hospital Zurich. *Diseases*, https://www.neoscreening.ch/de/krankheiten/ Updated: unclear	Full implementation since January 2019	10
United Kingdom 1. HIQA. *Review of NBS Policy-making processes*, July 2021 2. UK National Screening Committee, *SCID*, https://view-health-screening-recommendations.service.gov.uk/scid/, Updated: unclear 3. Public Health England Screening, *Newborn blood spot evaluation update — screening for SCID*, https://www.health.gov.au/health-topics/pregnancy-birth-and-baby/newborn-bloodspot-screening, Updated: September 2020	Under review/pilot	9
United States Currier and Puck. *SCID newborn screening: What we've learned,* 2021	SCID was added to the Recommended Uniform Screening Panel in 2010. Implemented in 50 and Puerto Rico	35 core conditions and 26 secondary conditions

*Implementation at a regional level

Appendix 4.1 Excluded studies relevant to analytical performance

Title	Author	Link
Time-dependent decline of T-cell receptor excision circle levels in ZAP-70 deficiency	Reid 2020	http://dx.doi.org/10.1016/j.jaip.2019.08.018
Retrospective TREC testing of newborns with Severe Combined Immunodeficiency and other primary immunodeficiency diseases	Jilkina 2014	http://dx.doi.org/10.1016/j.ymgmr.2014.07.003
Defining combined immunodeficiency	Roifman 2012	http://dx.doi.org/10.1016/j.jaci.2012.04.029
Screening of neonatal UK dried blood spots using a duplex TREC screening assay	Adams 2014	http://dx.doi.org/10.1007/s10875-014-0007-6
An evaluation of the TREC assay with regard to the integration of SCID screening into the Dutch newborn screening program	Blom 2017	http://dx.doi.org/10.1016/j.clim.2017.05.007
Newborn screening for severe combined immunodeficiency: Evaluation of a commercial T-cell receptor excision circle-based method in Victorian dried blood spots	Richards 2018	http://dx.doi.org/10.1111/jpc.13659
Newborn screening for severe T and B cell immunodeficiency in Israel: A pilot study	Amariglio 2013	PMID: 24079059
Implementation of SCID Screening in Denmark	Bækvad-Hansen 2021	http://dx.doi.org/10.3390%2Fijns7030054
Neonatal screening for severe combined immunodeficiency in Brazil	Kanegae 2016	http://dx.doi.org/10.1016/j.jped.2015.10.006
High incidence of severe combined immunodeficiency disease in Saudi Arabia detected through combined T cell receptor excision circle and next generation sequencing of newborn dried blood spots	Al-Dakheel 2018	http://dx.doi.org/10.3389/fimmu.2018.00782
Newborn screening for severe combined immunodeficiencies using trecs and krecs: Second pilot study in Brazil	Kanegae 2017	http://dx.doi.org/10.1590/1984-0462/;2017;35;1;00013
A Droplet Digital PCR Method for Severe Combined Immunodeficiency Newborn Screening	Vidal-Folch 2017	http://dx.doi.org/10.1016/j.jmoldx.2017.05.011
Evaluation of the T-cell receptor excision circle assay performances for severe combined immunodeficiency neonatal screening on Guthrie cards in a French single centre study	Audrain 2014	http://dx.doi.org/10.1016/j.clim.2013.11.012
Newborn screening for severe combined immunodeficiency using a novel and simplified method to measure T-cell excision circles (TREC)	Kunz 2017	http://dx.doi.org/10.1016/j.clim.2016.11.016
Prospective neonatal screening for severe T- and B-lymphocyte deficiencies in Seville	deFelipe 2016	http://dx.doi.org/10.1111/pai.12501
Development of a Multiplex Real-Time PCR Assay for the Newborn Screening of SCID, SMA, and XLA	Gutierrez-Mateo 2019	http://dx.doi.org/10.3390/ijns5040039
Newborn screening using TREC/KREC assay for	Nourizadeh 2018	http://dx.doi.org/10.11

severe T and B cell lymphopenia in Iran		11/sji.12699
Investigating the variation of TREC/KREC in combined immunodeficiencies	Shakerian 2021	http://dx.doi.org/10.18502/ijaai.v20i4.6950
Neonatal screening for severe primary immunodeficiency diseases using high-throughput triplex real-time PCR	Borte 2012	http://dx.doi.org/10.1182/blood-2011-08-371021

Appendix 4.2 Screening processes within studies of the accuracy of TREC-based screening for SCID

Study (year)	Punch size / DNA isolation	Platform and process	TREC cut off Method of establishment	Algorithm details	Prematurity considered	Confirmatory method	Diagnostic criteria
TREC: Population-based cohort studies							
Amatuni 2019[104] Additional reporting: Kwan 2013[153]	3.2 mm NR	Initially in-house assay during pilot up to June 2015. Following pilot, EnLite neonatal TREC kit used (PerkinElmer, Inc, Waltham, MA). RT-qPCR analysis. **Control gene:** Beta-actin	**Initial (up to June 2015):** TREC <25 copies/µL **Adjusted (June 2015 to February 2017):** TREC <22 copies/µL **Adjusted (February 2017 onwards):** TREC <18 copies/µL Initial validation tests with manufacturer recommendations and further refinement during study period.	TREC greater than threshold considered normal. If TRECs were below the threshold, a repeat punch for TRECs and an actin gene segment copy number determination was performed on the same specimen. TREC greater than threshold and beta-actin >35copies/µL (5000 copies/µL in pilot assay) and infant not in NICU: consider positive and refer (<4 copies/µL considered urgent positive). TREC greater than threshold and infant in NICU: considered incomplete, second DBS test requested.	No, however NICU admission is considered.	Flow cytometry and further tests as appropriate, including gene sequencing.	SCID: Infants with <300 CD3 T cells per mL of blood or with <2% of their helper T cells bearing the naïve T-cell marker CD45RA. Non-SCID lymphopenia: 300-1,500 circulating T cells per mL with naïve T cells present.

Study (year)	Punch size / DNA isolation	Platform and process	TREC cut off Method of establishment	Algorithm details	Prematurity considered	Confirmatory method	Diagnostic criteria
Argudo-Ramírez 2021[91] Additional reporting: Argudo-Ramírez 2019[143] and Martin-Nalda 2019[155]	1.5 mm DNA elution	EnLiteTM Neonatal TREC kit (PerkinElmer). Endpoint PCR. TREC and beta-actin gene amplification and hybridization followed by signal measurement with a Victor® EnLite fluorometer (PerkinElmer). **Control gene:** Beta-actin	**Initial (n = 66,811):** retest cut-off of 34 copies/µL and detection cut-off of 20 copies/µL (immediate referral if ≤10 copies/µL) **Adjusted (n = 156,046):** 24 copies/µL of TREC as retest cut-off and 20 copies/µL as detection cut-off (immediate referral if ≤10 copies/µL). Initial validation through pilot study with further refinement during study period.	24 copies/µL of TREC as retest cut-off and 20 copies/µL as detection cut-off (with beta-actin >50 copies/µL). On retest, full term newborns with a value of ≤10 copies/µL are referred to the hospital while a second sample is requested if TREC values are between 11 and 20 copies/µL. If TREC values in the second sample remain ≤20 copies/µL, the newborn is also referred to the hospital.	On retest, preterm newborns with ≤5 copies/µL are referred directly to the hospital as a positive screening. A second sample is requested if TREC values are between 6 and 20 copies/µL. If TREC values in the second sample remain lower than 20 copies/µL, the newborn is also referred to the hospital.	Flow cytometry T CD4+ and CD8+ (HLA-DR+). Recent thymic emigrants (CD3+ CD4+ CD27+ CD45RA+ CD31+) CD45RA/RO TCR αβ/γδ. In vitro lymphocyte proliferation assay IgG, IgA, IgM and IgE urine CMV. PID NGS-based gene panel for confirmed cases.	SCID: CD3 T <300 cells/µL <10% proliferation to PHA. Non-SCID: Lymphopenia without SCID criteria.

Study (year)	Punch size / DNA isolation	Platform and process	TREC cut off Method of establishment	Algorithm details	Prematurity considered	Confirmatory method	Diagnostic criteria
Cogley 2021[149]	3.2 mm DNA elution from DBS specimens using Extracta DBS (Quantabio, Beverly, MA, USA)	Lab-developed multiplex PCR assay measures both TREC and the survival motor neuron 1 gene to include SMA. Run on QuantStudioTM 5 PCR system (Thermo Fisher Scientific, Waltham, MA, USA). Detailed overview of primers, probes and targets. Ct values used to calculate multiple of the median (MoM).	Use Mutiple of the Median (MoM) based on Ct values: TREC MoM <1.079 are deemed to screen negative. Cut-off established based on initial 2244 samples.	Newborns with a TREC MoM <1.079 are deemed to screen negative for SCID. Newborns with a TREC MoM value >1.079 upon first analysis are retested in duplicate, with two new punches taken from the same specimen card. If both of these samples have a TREC MoM <1.079, the newborn is deemed to screen negative for SCID. If the repeat samples have a TREC MoM >1.079, DNA quality and quantity are assessed by analysis of the RPP30 MoM. If the RPP30 MoM >1.035, the screen is deemed inconclusive, and a repeat newborn screen is	See Algorithm details. Also, if repeat test is <1.079 and RPP30 MoM <1.035, with an adjusted age of <37 weeks, a repeat newborn screen is recommended.	Flow cytometry.	Based on flow cytometry reference ranges (not reported).

Study (year)	Punch size / DNA isolation	Platform and process	TREC cut off Method of establishment	Algorithm details	Prematurity considered	Confirmatory method	Diagnostic criteria
		Control gene: RPP30		recommended. If the RPP30 MoM <1.035, the screen is deemed positive, and the recommended action is based on the newborn's adjusted age. For newborns with an adjusted age of 37 weeks, confirmatory testing is recommended.			
Göngrich 2021[55]	3.2 mm DNA elution using MiniAmp Thermal Cyclers (Thermo Fisher Scientific, Waltham, MA, USA)	SPOTit-TK kit with multiplex assay in 96-well format (ImmunoIVD, Nacka, Sweden). PCR on Applied Biosystems QuantStudio 5 Dx instruments (Thermo Fisher Scientific, Waltham, MA,	**Initial (August 2019 to April 2020):** <15 TREC copies/well **Adjusted (April to August 2020):** <10 TREC copies/well Based on manufacturer recommendations and pilot	Samples were considered directly normal if TREC >15 copies/well (lowered > 10 copies/well, on 1 April 2020). TREC results below this cut-off were reanalysed in duplicate from different blood spots of the original screening card. If the initial TREC result was below the referral cut-off (≤6 copies/well), samples were	No	Fluorescence activated cell sorting (flow cytometry). Whole-genome sequencing (GMCK, Solna, Sweden).	Lymphopenia was defined as CD3+ T cells below 2 x 10^9 cells/L.

Study (year)	Punch size / DNA isolation	Platform and process	TREC cut off Method of establishment	Algorithm details	Prematurity considered	Confirmatory method	Diagnostic criteria
		USA). Internal controls noted. **Control gene:** Beta-actin	study results from Zetterstrom 2017.	analysed in quadruplicate. If all the replicate analyses yielded TREC ≤6 copies/well, and beta-actin levels were >1,000 copies/well, the child was referred. If samples had beta-actin levels <1,000 copies/well they were considered inconclusive and a new DBS card was requested.			
Hale 2021[105]	3.2 mm DNA elution by Luminex	Developed and validated a high throughput multiplex RT-qPCR assay. Forward and reverse primers targeting δRec-ψJα TREC target	<252 copies/μL. Initial validation study to establish cut-offs. Further refinement during study period.	Initially all infants with results out of range required repeat DBS or referral. After two years of screening, this was amended to require at least two out of range results (that is retesting). Further amended so that any infant with undetectable TREC on initial test was	No. However, considers NICU status in part.	Flow cytometry (a number diagnosed clinically in the absence of flow cytometry).	T-cell lymphopenia, defined as having a CD3 count <2,500 cells/μL. The diagnosis of SCID was made according to criteria of the Primary

Study (year)	Punch size / DNA isolation	Platform and process	TREC cut off Method of establishment	Algorithm details	Prematurity considered	Confirmatory method	Diagnostic criteria
		and RNaseP sequences. Internal controls noted. **Control gene:** RNaseP		immediately referred. Current algorithm for referral states that infants are referred for testing if they have undetectable TREC values on an initial NBS sample or if they have out-of-range TREC values (<252 copies/mL) on 2 serial specimens in the absence of a normal result.			Immune Deficiency Treatment Consortium including typical SCID, leaky SCID, and Omenn syndrome.
Kwan 2015[107]	3.2 mm NR	NR **Control gene:** Beta-actin	<25 copies/µL. Based on pilot study results.	Initial TREC >40 copies/µL considered normal. TREC<40 copies/µL retested with beta-actin. TREC<25 copies / µL and normal beta-actin considered normal. TREC undetectable and beta-actin>5,000 copies/µL - immediate referral. TREC undetectable and	TREC undetectable and beta-actin>5,000 copies/µL - immediate referral. For all cases with low TREC and inconclusive beta-actin, consider	Flow cytometry.	NR

Study (year)	Punch size / DNA isolation	Platform and process	TREC cut off Method of establishment	Algorithm details	Prematurity considered	Confirmatory method	Diagnostic criteria
				beta-actin<5,000 copies/µL and full term - request repeat DBS. TREC<25 copies/µL, full term, and beta-actin>10,000/µL - refer onwards. TREC<25 copies/µL, full term, and beta-actin <10,000/µL - request repeat DBS.	inconclusive and request repeat DBS at normal gestational age.		
Kwan 2014 - Colorado[106]	NR	Local assay. Quantitative PCR (qPCR). **Control gene:** Beta-actin	<40 TREC/µL. NR	Initial sample <40 TRECs/µL retested for TREC and beta-actin in duplicate using a new punch. Samples that upon repeat had <40 TRECs/µL and >8,000 beta-actin copies/µL were presumptive positive, and patients were referred to a clinical immunologist. Samples with <40 TRECs/µL and <8,000 beta-actin copies were	No.	Flow cytometry with further evaluation as appropriate.	T-cells <1500/µL

Study (year)	Punch size / DNA isolation	Platform and process	TREC cut off Method of establishment	Algorithm details	Prematurity considered	Confirmatory method	Diagnostic criteria
				inconclusive, and second dried blood spots were requested.			
Kwan 2014 - Connecticut[106]	NR	US CDC assay. Quantitative PCR (qPCR). **Control gene:** RNaseP	≤30 TREC/μL (urgent positive: ≤10 TREC/μL). NR	TREC copies <10/μL and RNaseP Ct <28 immediate referral. TREC cut-offs were ≤30/μL for term. Samples with RNaseP Ct ≥28 were unsatisfactory and additional dried blood spots were requested. TRECs between 10 and 30/μL required repeat TREC measurement in a new punch.	≤25 TREC/μL.	Flow cytometry with further evaluation as appropriate.	T-cells <1,500/μL <50 % CD4+/CD45RA + naïve T-cells/μL.
Kwan 2014 - Delaware[106]	NR	US CDC assay. Quantitative PCR (qPCR). **Control gene:** RNaseP	<27 TREC/μL (urgent positive: ≤16 TREC/μL). NR	Cut-offs were Borderline (17-26 TRECs), Abnormal (4-16 TRECs) and Alert (Undetectable - 3 TRECs). RNaseP values out of range were considered invalid.	Samples from preterm infants (<38 weeks) that were invalid, or had low TRECs, were repeated on a subsequent	Flow cytometry with further evaluation as appropriate.	T-cells <1,500/μL

Study (year)	Punch size / DNA isolation	Platform and process	TREC cut off Method of establishment	Algorithm details	Prematurity considered	Confirmatory method	Diagnostic criteria
					dried blood spot.		
Kwan 2014 - Michigan[106]	NR	Local assay. Quantitative PCR (qPCR). **Control gene:** Beta-actin	Repeat DBS: ≤11 TREC/μL (urgent positive ≤7 TREC/μL). NR	TRECs ≤7 copies/μL and beta-actin Ct ≤30 immediate referral. Samples with 7-11 TRECs/μL and beta-actin Ct ≤30 required a repeat sample. If a second dried blood spot also showed ≤11 TRECs/μL, the infant was referred.	No.	Flow cytometry with further evaluation as appropriate.	T-cells <3,505/μL
Kwan 2014 - Mississippi[106]	NR	PerkinElmer Genetics lab. Quantitative PCR (qPCR). **Control gene:** Beta-actin	≤25 TREC/ μL. NR	NR	No.	Flow cytometry with further evaluation as appropriate.	T-cells <2,500/μL.
Kwan 2014 - Texas[106]	NR	Local assay. Quantitative PCR (qPCR).	≤150 TREC/ μL. NR	Initial test <200 TRECs/μL were retested in duplicate. Final average TRECs ≤150 and RNaseP Ct ≤28.5 were reported	≤110 TREC/μL.	Flow cytometry with further evaluation as appropriate.	T-cells <1,500/μL.

Study (year)	Punch size / DNA isolation	Platform and process	TREC cut off Method of establishment	Algorithm details	Prematurity considered	Confirmatory method	Diagnostic criteria
		Control gene: RNaseP		as abnormal or borderline, while infants with undetectable TRECs and RNaseP Ct ≤28.5 were immediately referred. All other abnormal results required a request for additional sample.			
Kwan 2014 - Wisconsin[106] Additional reporting: Verbsky 2012[158]	3.2mm NR	Local assay. Quantitative PCR (qPCR). **Control gene:** Beta-actin	<30 TREC/μL NR	Initial test TREC <30 TREC/μL then tested with beta-actin. If the beta-actin level was normal with abnormally low TRECs then referred. If the beta-actin result was low then inconclusive and repeat sample requested.	<25 TREC/μL. Abnormal or inconclusive, the screening test was repeated until either normal or until the infant reached 37 weeks at which time the infant was referred.	Flow cytometry with further evaluation as appropriate.	T-cells <2,500/μL.
Rechavi 2017[108]	1.5 mm	EnLiteTM Neonatal TREC	**Initial:** <36 copies/μL	If low TREC identified retesting of two	No. However gestational	Immunofluorescent staining	SCID: less than 300/μl

Study (year)	Punch size / DNA isolation	Platform and process	TREC cut off Method of establishment	Algorithm details	Prematurity considered	Confirmatory method	Diagnostic criteria
	DNA elution	kit. qPCR (ABI PRISM 7900 Sequence Detector System (Applied Biosystems). **Control gene:** Beta-actin	**Adjusted:** <23 copies/µL Validation tests initially with refinement during study period.	additional punches taken from different DBS of the same card. If both are below cut-off for TREC with normal amplification of beta-actin (>16 copies/µL), second DBS requested tested. If all five tests returning positive infant referred.	birth weight 5 standard deviations above or below norm excluded from analysis.	and flow cytometry. T-cell proliferation. T-cell repertoire analysis. Whole exome sequencing or direct Sanger sequencing for SCID.	CD3+ T cells Leaky SCID: lymphopenia but >300/µl CD3+ T cells. Non-SCID lymphopenia: lymphopenia due to secondary causes, prematurity, or unknown aetiology
Vogel 2014[109]	3.2 mm DNA elution	RT-qPCR (Applied Biosystems). Detailed overview of primers, probes and targets. δRec-ψJα TREC target. Internal controls noted.	<200 copies/µL Based on validation work.	Initial results TREC> 200 copies/µL and RNaseP Cqs<35 considered normal. TREC≤200 copies/µL and RNaseP Cqs<35 retest in duplicate. RNaseP Cqs>35 considered failure and repeat DBS requested. TREC TREC≤200 copies/µL, RNaseP normal on retest and full term, immediate	TREC detectable and ≤200 copies/µL with RNaseP normal, request repeat DBS at normal gestational age. TREC undetectable denotes	Flow cytometry. T-cell activation with mitogens, chromosome analysis and genetic testing performed as appropriate.	Based on clinical interpretation in absence of defined case definitions at time of study.

Study (year)	Punch size / DNA isolation	Platform and process	TREC cut off Method of establishment	Algorithm details	Prematurity considered	Confirmatory method	Diagnostic criteria
		Control gene: RNaseP		referral. TREC 125-200 copies/µL, RNaseP Cqs<35, and full term considered borderline and request repeat DBS.	immediate referral.		
TREC: Pilot cohort studies							
Audrain 2018[145] Additional reporting: Audrain 2021[144] and Thomas 2019[157]	1.5 mm DNA elution	EnLite Neonatal TREC in vitro diagnostic kit (PerkinElmer). End point PCR. After TREC and beta-actin amplification and hybridization with probes, the Victor Enlite™ fluorometer was used to measure probe fluorescence.	**Initial (n = 118,106):** <11 copies/µL immediate referral. <35 copies/µL repeat test. <21 copies/µL repeat DBS. **Adjusted (n = 72,411):** <11 copies/µL immediate referal. <21 copies/µL repeat test and repeat DBS if persists. Cut-off established from 3451 initial	**Initial (n = 118,106):** Result<11 copies/µL, immediate referral. Result <35 copies/µL, analyses of two additional punches from the same DBS card performed. TREC counts for 2/ 3 punches were <21 copies/µL, sample presumed positive if beta-actin amplification present or repeat DBS requested if inconclusive results beta-actin <35.	Result of <6 copies/µL led to immediate referral, while TREC levels between 6 and 21 request repeat DBS. Reduced to <5 copies/µL after readjustment .	Paediatric referral and flow cytometry.	Lymphopenia: < 2,500 T cells/µL SCID: T cell count persistently below 300/µL with no naive T-cells.

Study (year)	Punch size / DNA isolation	Platform and process	TREC cut off Method of establishment	Algorithm details	Prematurity considered	Confirmatory method	Diagnostic criteria
		Internal controls noted. **Control gene:** Beta-actin	samples. Additional refinement during study period.	**Adjusted protocol (n = 72,411):** Due to high recall rate. Results <11 copies/µL led to immediate referrals. Second tests if results <21 copies/µL beta-actin>35. Repeat DBS if persists. Inconclusive results if beta-actin <35.			
Blom 2021a[146] Additional reporting: Blom 2021b[147]	3.2 mm DNA elution	SPOT-it kit (ImmunoIVD, 14 Stockholm, Sweden). QuantStudio 5 qPCR system 19 (Thermo Fisher, Waltham, Massachusetts, USA). **Control gene:** Beta-actin	**Initial (April 2018 to October 2018):** ≤ 6 copies/3.2mm **Adjusted (November 2018 to February 2018):** ≤ 10 copies/3.2mm Initial validation undertaken with further	Initial TREC greater than cut-off then presumed normal. Initial TREC less than cut-off then retest two additional punches from DBS. If one (or both) duplicates ≤10 copies/3.2 mm punch and beta-actin >1000 and full terms then refer. If beta-actin ≤1000 then retest in duplicate again. If 2/5 total beta-actin >1000 and full term then	Throughout algorithm, if abnormal results from preterm infant (≤ 37 gestational weeks and birth weight ≤2500 grams) then request repeat DBS at 37 weeks.	Flow cytometry whole-exome sequencing with gene panel (37 genes included in SCID gene panel) analysis as appropriate. Flow cytometry included analysis of CD3+ T-cells, CD4+ and CD8+ T-cells,	Low or abnormal: T-cells ≤1500 CD3+/µl > 200 naive/µl Absent: naive T-cells ≤200/µl

Study (year)	Punch size / DNA isolation	Platform and process	TREC cut off Method of establishment	Algorithm details	Prematurity considered	Confirmatory method	Diagnostic criteria
			refinement during the study period.	refer. If beta-actin>1000 and full term request second DBS sample.		CD56/16 NK-cells and CD19 B-cells and T-cell subsets CD45RA/CD45 RO (%) naïve T-cells.	
Chien 2015[148]	3.2 mm Generation DNA elution solution (QIAGEN)	RT-qPCR (by TaqMan Gene Expression Master Mix, Applied Biosystems). **Control gene:** RNaseP	<40 TRECs/µL Based on previous studies.	DBS with a zero TREC value but a normal RNaseP value were defined as abnormal. DBS with a TREC value between zero and 40 was defined as inconclusive. All inconclusive DBSs required a repeat DBS, and either a low or zero TREC value on the repeat DBS was defined as abnormal.	No.	Flow cytometry. For a DBS with an abnormal or inconclusive screening result, TUPLE1 gene copy number analysis for chromosome 22q11.2 microdeletion syndrome was performed.	NR
Kwan 2015[107]	3.2 mm Samples underwent organic extraction	Laboratory developed assay. RT-qPCR (Applied	<33 copies/µL. Based on validation work.	TREC value above cut off on initial or repeated test considered normal. Abnormal tests repeated with beta-	No.	Flow cytometry	NR

Study (year)	Punch size / DNA isolation	Platform and process	TREC cut off Method of establishment	Algorithm details	Prematurity considered	Confirmatory method	Diagnostic criteria
	with DNA precipitation.	Biosystems). Detailed information provided on primers, probes and targets. Internal controls noted. **Control gene:** Beta-actin		actin control. TREC value low on initial or repeated test with normal beta-actin considered positive. TREC low with low beta-actin considered inconclusive and repeat DBS requested.			
TREC: Referral-based studies							
Gans 2020[150]	NR	NR	TREC <200 copies/µL. NR	TREC <200 copies/µL considered positive and referred onwards.	NR	Repeat TREC assay, complete J24:K25 blood count. Flow cytometry for lymphocyte subsets, and mitogen-induced lymphocyte proliferation.	Full-term infants were considered lymphopenia if absolute cell counts of CD3, CD4, CD8, or CD19 were below the following normal reference values

Study (year)	Punch size / DNA isolation	Platform and process	TREC cut off Method of establishment	Algorithm details	Prematurity considered	Confirmatory method	Diagnostic criteria
						Genetic studies as appropriate.	for ages 0-2 months: CD3 2,500-5,500 cells/µL, CD4 1,600-4,000 cells/µL, CD8 560-1,700 cells/µL, CD19 300-2,000 cells/µL.
Mantravadi 2021[154]	NR	NR	Illinois: < 250 copies/µL Missouri: cycle threshold value of 37 or greater NR	A positive screen in Illinois was defined as a TREC level of 250 copies/µL or less, and in Missouri as a cycle threshold value of 37 or greater. Cycle thresholds greater than 39 or TREC levels less than 25 copies/µL were considered high risk and resulted in immediate referral for further workup instead of repeating the newborn screen.	NR	Complete blood count with differential, quantitation of lymphocyte subpopulations, TREC copy number analysis normalized to CD3+ T cell count, absolute CD4RTE, and naïve Th cell percentage. Results of	Typical SCID: CD3+ T cells < 300 cells/µL, less than 10% of the lower range of normal proliferation to phytohaemagglutinin, and/or detectable maternal T cell engraftment. Leaky SCID: CD3+ T-cell count of >300 cells/µL, but with a

Study (year)	Punch size / DNA isolation	Platform and process	TREC cut off Method of establishment	Algorithm details	Prematurity considered	Confirmatory method	Diagnostic criteria
						chromosome microarray, targeted gene panels, and whole exome sequencing were also reviewed if obtained for clinical care.	restricted TCR repertoire and/or lack of naive T cells. Non-SCID TCL: CD3+ T cells < 2,500 cells/μL.
Thorsten 2021[64]	3.2mm NR	RT-qPCR.	Multiple changes over study duration. NR	If the specimen falls below the screening TREC level cut-off, two more punches are obtained rendering three separate TREC levels. Note there has been several changes to cut off used over study period.	Separate diagnostic pathway.	Flow cytometry T-cell proliferation.	Typical SCID: CD3+ T cell number <300/μL and phytohaemagglutinin mitogen response <10% of the lower limit of normal Leaky SCID: absence of maternal lymphocytes and PHA mitogen

Study (year)	Punch size / DNA isolation	Platform and process	TREC cut off Method of establishment	Algorithm details	Prematurity considered	Confirmatory method	Diagnostic criteria
							response <30% of lower limit of normal and CD3 count <1,500/µL Omenn syndrome: CD3+ T cell number (> 300/µL), PHA mitogen response <30% of lower limit of normal, and/or generalized erythroderma in the absence of maternal engraftment. Non-SCID TCL: CD3+ T cell number that was below the age adjusted 10th percentile

Study (year)	Punch size / DNA isolation	Platform and process	TREC cut off Method of establishment	Algorithm details	Prematurity considered	Confirmatory method	Diagnostic criteria
TREC with KREC							
Gizewska 2020[151] – Pilot	3.2 mm DNA elution	SPOT-it TM TK (ImmunoIVD, Sweden). qPCR (QuandStudio 5 Thermo Science). **Control gene:** Beta-actin	TREC: <6 copies/µL KREC: <4 copies/Ml NR	In the case of abnormal results (TREC <6 copies/µL and/or KREC <4 copies/µL) or inconclusive results (beta-actin <1,000 copies/µL), retested in duplicate from same DBS. Follow on procedure depends on the values obtained from the first screening card (3 punches). Numbers of TREC and/or KREC <1 copies/µL in the retest resulted in immediate referral. When the value of TREC was in range of 1-4 and/or KREC 1-6 copies/µL request second blood sample.	In the case of extremely and very preterm newborns (born <32 weeks) the second screening cards were taken when the child reached 32-34 weeks of gestational age.	Immunocytometry assay, recent thymic emigrants, lymphocyte proliferation tests, humoral immunity adjustment (immunoglobulin levels), cytogenetic tests (karyotype), molecular tests (Generation Sequencing or single gene sequencing by Sanger), and, if available and needed, radiosensitivity tests, TCR V beta repertoire,	SCID defined as T-cells <300 cells/µL

Study (year)	Punch size / DNA isolation	Platform and process	TREC cut off Method of establishment	Algorithm details	Prematurity considered	Confirmatory method	Diagnostic criteria
						ADA and PNP enzyme activity levels, and anthropometry.	
Kutlug 2021[152] – Pilot	3.2 mm DNA elution	Diagnostic neonatal screening kit for primary immunodeficiency diseases was used (ImmunoIVD, Stockholm, Sweden). PCR on the Applied Biosystems 7500 Fast Real-Time PCR System. Internal controls noted. **Control**	TREC: <7 copies/µl KREC: <7 copies/µl Based on initial validation and previous studies.	Beta-actin copies ≥1,000/µl and TRECs or KRECs copies <7 µl, the test was assumed positive or abnormal. In cases of TRECs and KRECs >7/µl, regardless of beta-actin value, the test was assumed normal. In cases of beta-actin <1,000/µl and TRECs or KRECs copies <7/µl, the test was assumed inconclusive. Samples with TREC and or KREC <7 copies/µl and beta-actin >1,000/µl retested in duplicate.	No	Immunophenotyping, T-cell proliferation, flow cytometry, next generation sequencing as appropriate.	SCID: absence of T-cells or CD3 T cells <300/µL and no or very low T-cell function (<10% of lower limit of normal) as measured by response to PHA. Non-SCID T-cell lymphopenia CD3 T-cells 300-1,500/µL.

Study (year)	Punch size / DNA isolation	Platform and process	TREC cut off Method of establishment	Algorithm details	Prematurity considered	Confirmatory method	Diagnostic criteria
		gene: Beta-actin					
Zetterstrom 2017[159] – Pilot Additional reporting: Barbaro 2017[54]	3.2 mm DNA elution using Generation DNA Elution Solution (QIAGEN).	Quantitative triplex PCR on a Viia7 Real-time PCR system (Applied Biosystems, Foster City, CA, USA). **Control gene:** Beta-actin	TREC: < 25 copies/3.2 mm punch KREC: <15 copies/3.2 mm punch Based on previous validation studies.	Repeat tests performed if TREC < 25 copies/3.2 mm punch and or KREC <15 copies/3.2 mm punch. Values of beta-actin were considered only in case of TREC and or KREC values below cut-off for repeat test. If beta-actin <1000/copies then retest and if persists consider inconclusive and request new sample. All samples with TREC and or KREC below retest cut off and normal beta-actin referred.	No	Repeat sample taken and other investigations as decided by Paediatrician including flow cytometry and genetic analysis.	NR
TREC with NGS							
Strand 2020[156] - Pilot	3.2 mm DNAelutio	RT-qPCR on ViiA7 and QuantStudio 7 (Applied	<25 TRECs/μL. NR	Samples <25 TRECs/μL retested with one repunch on DBS. On retest	On retest samples with normal levels of beta-actin	Second tier next generation sequencing	Detailed overview of targets but no

Study (year)	Punch size / DNA isolation	Platform and process	TREC cut off Method of establishment	Algorithm details	Prematurity considered	Confirmatory method	Diagnostic criteria
	n (QIAGEN)	Biosystems/Thermo Fisher Scientific, CA, USA). Detailed primer, probe and target information presented. **Control gene:** Beta-actin		samples with normal levels of beta-actin (≥ 5,000/μL), <20 TRECs/μL and full term tested with gene panel. Inconclusive and retests >20 TRECs/μL request repeat DBS.	(≥ 5,000/μL), <15 TRECs/μL tested with gene panel. Inconclusive and retests >15 TRECs/μL request repeat DBS.	built into algorithm with follow-up immunological tests (including flow cytometry and CMV status) as appropriate.	cut offs provided.
Strand 2020[156] - Population	3.2 mm DNA elution (QIAGEN)	RT-qPCR on ViiA7 and QuantStudio 7 (Applied Biosystems/Thermo Fisher Scientific, CA, USA). Detailed primer, probe, and target information presented.	<25 TRECs/μL. Based on pilot study results.	Samples <25 TRECs/μL retested with two repunches on DBS. On retest samples with normal levels of beta-actin (≥ 5,000/μL), <25 TRECs/μL and full term tested with gene panel. Inconclusive and negative gene panel request repeat DBS.	On retest samples with normal levels of beta-actin (≥ 5,000/μL), <15 TRECs/μL tested with gene panel. Inconclusive and negative gene panel request repeat DBS.	Second tier next generation sequencing built into algorithm with follow-up immunological tests (including flow cytometry and CMV status) as appropriate.	Detailed overview of targets but no cut offs provided.

Study (year)	Punch size / DNA isolation	Platform and process	TREC cut off Method of establishment	Algorithm details	Prematurity considered	Confirmatory method	Diagnostic criteria
		Control gene: Beta-actin					

Key: ADA - adenosine deaminase; CD - cluster of differentiation; CMV - cytomegalovirus; DBS - dried bloodspot; DNA - deoxyribonucleic acid; Ig(A or D or E or G or M) - immunoglobulin; KREC - kappa-deleting recombination excision circles, MoM - Mutiple of the Median; NGS - next generation sequencing; NICU - neonatal intensive care unit; NR - not reported; PHA - phytohemagglutinin; PID - primary immunodeficiency; PNP - purine nucleoside phosphorylase; TCR - T-cell receptor; TREC - T-cell receptor excision circles; RT-qPCR - quantitative reverse transcription polymerase chain reaction; SMA - spinal muscular atrophy.

Notes: Cluster of differentiation or "CD" followed by a number refers to proteins found on the surface of cells. Surface expression of a particular CD molecule is useful for identifying cell phenotypes.

PHA is used to trigger activation and proliferation of lymphocytes in vitro.

Appendix 4.3 SCID subtypes, TCL causes and missed cases documented within studies included in this report*

Study (year)	SCID subtypes**	Atypical SCID subtypes	TCL causes (excluding prematurity)	Missed cases
TREC: Population-based cohort studies				
Amatuni 2019[104, 153]	**Total (n=39)** IL2RG (n=14) ADA (n=8) RAG1 (n=2) IL7R (n=6) JAK3 (n=3) RAG2 (n=2) Unknown (n=4)	**Total (n=11)** ADA (n=1) RAG1 (n=3) Omenn syndrome RAG1 (n=3) RAG2 (n=1) BCL11B (n=1) RMRP (n=1) Unknown (n=1)	**Total (n=130)** **Congenital syndromes (n=72)** DiGeorge (n=47) Trisomy 21 (n=8) Ataxia telangiectasia (n=5) CHARGE syndrome (n=3) Diabetic embryopathy (n=3) CLOVES syndrome (n=1) EXTL3 deficiency (n=1) Fryns syndrome (n=1) Nijmegen syndrome (n=1) Noonan syndrome (n=1) RAC2 deficiency (n=1) **Secondary (n=25)** Congenital heart disease (n=6) Hydrops (n=6) Gastroschisis (n=4) Chylothorax (n=2) Maternal immunosuppressive medication (n=2) Third-space fluid leakage (n=2) Intestinal atresia (n=1) Meconium ileus (n=1) Teratoma of the thymus (n=1)	Although no cases of typical SCID are known to have been missed, two infants with delayed-onset leaky SCID had normal neonatal TREC screens but came to clinical attention at 7 and 23 months of age.

Study (year)	SCID subtypes**	Atypical SCID subtypes	TCL causes (excluding prematurity)	Missed cases
			Idiopathic (n=33) Resolved (n=11) Improving at time of study (n=2) Persistent (n=13) Unknown/death/lost to follow-up (n=7)	
Argudo-Ramírez 2021[91, 143, 155]	**Total (n=3)** RAG2 (n=1) PNP (n=1) Unknown (n=1)	NA	**Total (n=21)** **Syndrome (n=9)** DiGeorge (n=8) Down's syndrome (n=1) **Idiopathic (n=5)** Transient (n=1) Other (n=4) **Secondary (n=2)** Chylotorax (n=2) **Ongoing investigation (n=5)** One suspected leaky SCID	To the best of the authors' knowledge no SCID or clinically significant T-cell lymphopenia were missed.
Cogley 2021[149]	**Total (n=1)** RAG1 (n=1)	NA	**Total (n=22)** **T-cell lymphopenia (idiopathic, secondary, or transient) (N=13)** **Syndromes (n=9)** 22q11.2 deletion (n=5) Cartilage-hair hypoplasia (n=2) CHARGE syndrome (n=1)	NR

Study (year)	SCID subtypes**	Atypical SCID subtypes	TCL causes (excluding prematurity)	Missed cases
			Ataxia telangiectasia (n=1)	
Göngrich 2021[55]	**Total (n=3)** JAK3 (n=2) ADA (n=1)	NA	**Total (n=28)** **Genetic syndromes (n=9)** 22q11 deletion syndrome (n=4) CHARGE syndrome (n=1) Other syndromes(n=4) **Secondary causes: (n= 9)** Chylothorax (n=2) Hydrops (n=1) Postnatal sepsis (n=1) Juvenile myelomonocytic leukaemia (n=1) Unknown cause (n=4). **Group separately as false positives but with cause provided (n=10)** Genetic syndromes (n=6) Hydrops (n=1) Chylothorax (n=1) Maternal immunosuppressants (n=1) Older child with Hepatitis A and B infection (n=1)	Not informed of any SCID cases since study period, however informed of the birth of one child with combined immunodeficiency (MHC class II deficiency) who was not detected by the screening.
Hale 2021[105]	**Total (n=7)** JAK3 (n=1) IL2RG (n=2) TTC7A (n=1)	**Total (n=2)** JAK3 (n=1) ILR7 (n=1)	**Total (n=133)** **Combined immunodeficiency (n=7)** **Syndromes (n= 60):**	No infants with SCID have subsequently been identified.

Study (year)	SCID subtypes**	Atypical SCID subtypes	TCL causes (excluding prematurity)	Missed cases
	ADA (n=1) CD3D (n=1) RAG1 (n=1)		Complete DiGeorge (n=2) Partial DiGeorge (n=38) CHARGE (n=3) Jacobson (n=4) Trisomy 21 (n=8) Other (n=5) **Secondary (n=34)** Congenital heart disease (n=19) Lymphocyte loss (n=3) Heart disease (n=3) Other (n=8) **Benign/idiopathic (n=32)**	
Kwan 2015[107]	**Total (n=4)** Artemis-DCLRE1C (n=4)	NA	NA	NR
Kwan 2014 - Colorado[106]	NR	NR	NR	NR
Kwan 2014 - Connecticut[106]	NR	NR	NR	NR
Kwan 2014 - Delaware[106]	NR	NR	NR	NR
Kwan 2014 - Michigan[106]	NR	NR	NR	NR
Kwan 2014 - Mississippi[106]	NR	NR	NR	NR
Kwan 2014 - Texas[106]	NR	NR	NR	NR

Study (year)	SCID subtypes**	Atypical SCID subtypes	TCL causes (excluding prematurity)	Missed cases
Kwan 2014 - Wisconsin[106, 158]	NR	NR	NR	NR
Rechavi 2017[108]	**Total (n=5)** DCLRE1 (n=2) IL7Rα (n=1) DiGeorge (n=1) RMRP (n=1) **NOTE:** DiGeorge and RMRP classed as CID by IUSI	**Total (n=3)** DCLRE1 (n=2) IL7Rα (n=1)	**Total (n=18)** **Syndromes (n=9)** Down syndrome (n=4) partial DiGeorge syndrome (n=2) multiple congenital anomalies (n=1) Unknown (n=2) **Secondary (n=4)** chylothorax (n=3) Maternal medication (n=1) **Idiopathic (n=5)** All resolved by one year	No typical SCID patients have been reported in Israel since the initiation of the screening program.
Vogel 2014[109]	**Total (n=9)** IL7R (n=1) IL2RG (n=3) ADA (n=2) Unknown (n=3)	**Total (n=1)** IL2RG (n=1)	**Total (n=87)** **Idiopathic T cell lymphopenia (n=30)** Resolved (n=11) Persistent (n=19) **Syndromes (n=27)** DiGeorge (n=18) Down's Syndrome (n=4) 17q12 duplication syndrome (n=1) Trisomy 18 (n=1) 6p deletion syndrome (n=1) Ring chromosome 17 (n=1)	No notified cases up to time of writing.

Study (year)	SCID subtypes**	Atypical SCID subtypes	TCL causes (excluding prematurity)	Missed cases
			CHARGE (n=1) **Secondary (n=17)** Variable but majority had major birth defects including hypoplastic left heart syndrome, congenital diaphragmatic hernia and gastroschisis. **Other (n=13)**	
TREC: Pilot cohort studies				
Audrain 2018[144, 145, 157]	**Total (n=3)** ILRG (n=1) RAG2 (n=1) Unknown (n=1)	**Total (n=3)** ADA (n=1) TTC7A (n=1) RAG1 (n=1)	**Total (n=49)** **Secondary (n=15)** Cardiac malformations (n=7) Multiple malformations (n=4) Maternal medication (n =2) Chylous ascites (n=1) Comorbidities (n=1) **Syndromes (n=7)** DiGeorge (n=4) Down's (n=2) ATM mutation (n=1) **Idiopathic (n =27)** Transient (n=8) Moderate (n=19)	None reported over course of study.
Blom 2021a[146, 147]	**Total (n=1)** IL2RG (n=1)	NA	**Total (n=41)** **Syndromes (n=8)**	NR

Study (year)	SCID subtypes**	Atypical SCID subtypes	TCL causes (excluding prematurity)	Missed cases
			22q11.2 deletion syndrome (DiGeorge) (n=4) Trisomy 21 (n=2) Noonan syndrome (n=1) Heterozygous FOXN1 variant (n=1) **Secondary causes (n=28)** Multiple congenital anomalies (n=7) Congenital diaphragmatic hernia (n=3) Cardiac anomalies (n=2) Gastrointestinal anomalies (n=2) Chylothorax and hydrops (n=1) Sepsis/severe infections (n=6) Maternal immunosuppressant (n=3) Other neonatal conditions (including severe asphyxia, dysmaturity, high doses of dexamethasone) (n=4) **Idiopathic T-cell lymphopenia (n=5)**	
Chien 2015[148]	**Total (n=2)** IL2RG (n=1) RAG1 (n=1)	NA	**Total (n=16)** **Genetic (n=6)** Variant SCID (n=2) 22q11.2 deletion syndrome (n=4) **Secondary (n=10)** Chylothorax (n=1) Congenital heart disease (n=5) Congenital cytomegalovirus	NR

Study (year)	SCID subtypes**	Atypical SCID subtypes	TCL causes (excluding prematurity)	Missed cases
			infection with pancytopenia (n=1) Extremely low birth weight (n=3)	
Kwan 2015[107]	NA	NA	**Total (n=1)** Congenital anomalies (n=1)	NR
TREC: Referral-based studies				
Gans 2020[150]	**Total (n=2)** IL2RG (n=2)	**Total (n=1)** PNP (n=1)	**Total (n=53)** **Syndromes (n=9)** DiGeorge (n=6) Noonan syndrome (n=1) Alagille syndrome (n=1) LIS1-associated lissencephaly (n=1) **Idiopathic lymphopenia (n=44)**	NR
Mantravadi 2021[154]	**Total (n=6)** JAK3 (n=2) ADA (n=2) IL2RG (n=2)	**Total (n=3)** RAG1 (n=1) DOCK2 and Artemis (n=1) Unknown (n =1)	**Total (n=52)** **Non-SCID TCL with genetic or secondary cause (n =27)** Complete DiGeorge (n=1) 22q11 deletion (n=16) Trisomy 21 (n=2) Congenital thoraco-cervical fibrosarcoma (n=1) Genetic variants presumed to be pathogenic in TBX1 (n=2), FOXN1 (n=1), MYSM1 (n=1), CD3E (n=1), ATM (n=1), and POLD1 (n=1) **Idiopathic non-SCID TCL (n =25)**	One infant with leaky SCID who is not included in the study was found to have an IL2RG mutation despite a normal newborn SCID screen.

Study (year)	SCID subtypes**	Atypical SCID subtypes	TCL causes (excluding prematurity)	Missed cases
			Moderate (n=5) Mild (n=20)	
Thorsten 2021[64]	**Total (n=4)** IL2RG (n=1) ADA (n=1) RMRP (n=1) Unknown (n =1)	**Total (n=4)** FOXN1 (n=1) Unknown(n=1) Omenn syndrome (n=2)	**Total (n=26)** **Syndromes (n=14)** 22q11.2 deletion syndrome (n=5) Cartilage hair hypoplasia (n=2) Ataxia telangiectasia (n=2) Trisomy 21 (n=1) Ectrodactyly ectodermal dysplasia syndrome (n=1) Uncharacterized syndrome (n=3) **Secondary (n=2)** Chylothorax (n=2) **Idiopathic (n=10)** Resolved (n=4) Persistent (n=6)	NR
TREC with KREC				
Gizewska 2020[151] – Pilot	**Total (n=1)** T-B-NK+ SCID with severe cartilage-hair hypoplasia (homozygous	NA	**Total (n=5)** **Sydromes (n=3)** Atypical T-B-NK+ CID without dysmorphic features and of unknown genetic defect (n=1) Autosomal recessive agammaglobulinemia (n=1)	NR

Study (year)	SCID subtypes**	Atypical SCID subtypes	TCL causes (excluding prematurity)	Missed cases
	mutation in RMRP)		Nijmegen breakage syndrome (n=1) **Secondary (n=1)** Maternal immunosupression (n=1) **Transient with no genetic defect (n=1)**	
Zetterstrom 2017[159] – Pilot Additional reporting: Barbaro 2017[54]	NA	NA	TCL (n=3)	NR
Kutlug 2021[152] – Pilot	**Total (n=2)** DLCLRE1C (n=1) ADA (n=1)	NA	**Total (n=24)** Combined immunodeficiency (n=3) Maternal immunosuppression (n=19, 18 of which based on KREC) Trisomy 21 (n=2)	Since study period have not been informed of any additional PID cases in the screened cohort.
TREC with NGS				
Strand 2020[156] - Pilot	**Total (n=2)** IL2RG (n=1) RMRP (n=1)	**Total (n=1)** RAG2 (n=1)	**Total (n=15)** DiGeorge (n=1) Intestinal malformations (n=7) Congenital Heart Disease (n=4) Lung Disease (n=1) Other causes (n=2)	NR
Strand 2020[156] - Population	**Total (n=3)** DCLRE1C (n=1)	NA	**Total (n=NR)** Nijmegen breakage syndrome (n=1)	No other children born within the study time period have yet been

Study (year)	SCID subtypes**	Atypical SCID subtypes	TCL causes (excluding prematurity)	Missed cases
	JAK3 (n=1) IL2RG (n=1)		Trisomy 21 (n=2) Spink5 Netherton syndrome (n=1) Congenital aplasia (n=1) Born at term with normal weight and no pathogenic variants detected (n=6) Unknown clinical history (n=2) Other secondary clinical causes without pathogenic variant detected (n=15)	referred for SCID or severe T cell deficiency up to the time of writing.

Key: CID - combined immunodeficiency; MHC - major histocompatibility complex; NR - not reported; PID - primary immunodeficiency; TCL - T-cell lymphopenia; TREC - T-cell receptor excision circles.

*findings are reported as per original studies

** See section 3.1.1 for a description of SCID subtypes

Appendix 5.1 Supplementary characteristics of included studies

Table A5.1 Sex and ethnicity of study participants

Study	Sex		Ethnicity						
	Male	Female	White	Hispanic	Black	American Indian	Asian	Arabic	Not specified
Brown 2011[170]	NR	NR	NR	NR	NR	NR	NR	NR	NR
Dell Railey 2009[133]*	88	23	90	7	10	2	1	1	0
Myers 2002[173]*	74	18	77	8	6	1	0	0	0
Antoine 2003[175]	NR	NR	NR	NR	NR	NR	NR	NR	NR
Buckley 1999[168]	75	14	69	10	10	0	0	0	0
Buckley 2000[166]	NR	NR	NR	NR	NR	NR	NR	NR	NR
Buckley 2011[167]	NR	NR	NR	NR	NR	NR	NR	NR	NR
Chan 2011[171]	NR	NR	NR	NR	NR	NR	NR	NR	NR
Gennery 2010[172]	NR	NR	NR	NR	NR	NR	NR	NR	NR
Haddad 2018[118]	471	191	NR	NR	NR	NR	NR	NR	NR
Heimall 2017[122]**	61	39	43	20	9	0	11	0	17
Lankester 2021[136]	225	113	NR	NR	NR	NR	NR	NR	NR
Miyamoto 2021[131]	NR	NR	NR	NR	NR	NR	NR	NR	NR
Pai 2014[121]	173	67	118	67	25	8	9	0	13
Dvorak 2017[174]	49	34	NR	NR	NR	NR	NR	NR	NR

Key: NR – not reported

* Reported only for the SCID patients that survived to follow-up.

** Based on full overall study sample, only 98 of 100 patients subsequently received HSCT.

Table A5.2 Number of patients by conditioning regimen, where reported

Study	RIC	MAC	IS/None	Other (non-specified)	NR
Brown 2011[170]	27	30	31	0	20
Dell Railey 2009[133]	0	0	161	0	0
Myers 2002[173]	NR	NR	NR	NR	117
Antoine 2003	NR	NR	205	NR	270*
Buckley 1999[168]	NR	NR	NR	NR	89
Buckley 2000[166]	NR	NR	NR	NR	112
Buckley 2011[167]	NR	NR	151	4	11
Chan 2011[171]	NR	NR	NR	NR	158
Gennery 2010[172]	29	297	285	88	0
Haddad 2018[118]	69	148	439	6	0
Heimall 2017[122]	32	29	37	0	0
Lankester 2021[136]	32	163	137	0	6
Miyamoto 2021[131]**	0	62	79	28	12
Pai 2014[121]	35	46	159	0	0
Dvorak 2017[174]	17	Combined with RIC	66	0	0

Key: IS – immunosuppression therapy, MAC – myleoablative conditioning, NR – not reported, RIC – reduced intensity conditioning

* Study reports that 'most' patients who received conditioning received busulphan (8 mg/kg) and cyclophosphamide (200 mg/kg).

** Based on overall study sample (n=181). Age at HSCT was reported for 75 patients only.

Table A5.3 Number of infants according to SCID subtypes in included studies, where reported

SCID subtype	Antoine 2003[175]	Brown 2011[170]	Buckley 1999[168]	Buckley 2000[166]	Buckley 2011[167]	Chan 2011[171]	Dell Railey 2009[133]	Gennery 2010[172]	Haddad 2018[118]	Heimall 2017[122]	Lankester 2021[136]	Miyamoto 2021[131]	Myers 2002[173]	Pai 2014[121]
ADA	51	9	13	17	24	16	16	75	45	3	43	6	16	14
AK2 (Reticular Dysgenesis)	12	-	-	-	-	-	-	19	1	2	9	1	-	-
CD3 (δ, ε, Z)	-	-	-	-	4	-	4	-	7	3	7	2	-	3
DCLRE1C (Artemis)	-	2	-	-	2	-	-	-	28	3	34	6	-	11
IL2RG (X-linked)	-	11	43	54	75	58	53	-	187	33	109	55	55	86
IL7Rα	-	2	2	3	24	4	15	-	40	9	20	-	2	22
JAK3	-	4	6	6	9	3	6	-	24	5	26	3	5	11
LAT	-	-	-	-	-	-	-	-	-	-	2	-	-	-
LIG1/LIG4	-	-	-	-	-	-	-	-	-	1	3	3	-	-
PNP	-	-	-	-	-	1	-	-	1	-	3	-	-	1
PTPRC (CD45 deficiency)	-	-	-	-	1	1	1	-	1	-	-	-	-	1
RAG1/RAG2	-	7	-	-	7	9	6	-	52	25	78	14	3	17
ZAP-70	-	-	-	-	-	4	-	-	-	1	1	-	-	-
Unknown	-	9	20	5	19	-	9	-	276	13	-	-	21	74
Not specified	412**	-	-	26	-	26	-	605**	-	-	-	10	-	-
Omenn syndrome	-	2	-	-	-	4	-	-	-	-	-	-	-	-
Other*	-	-	-	1	1	-	-	-	-	2	3	-	1	-

* Includes: Cartilage hair hypoplasia, TTC7R, and XLF1., ** The data reported by Antoine et al. (2003) and Gennery et al. (2010) were primarily grouped by SCID phenotype. Antoine et al. reported that 137 infants were low T and low B, 217 were low T, and 58 were "other". Gennery et al. reported that 345 infants were T- B+ NK- (including ILR2G, JAK3, IL7Ra), and 206 were T- B- NK+ (including RAG 1, RAG 2, DCLRE1C). As the individual subtypes are not provided for these phenotypes, we present these data in the "not specified" category.
Note: Dvorak et al. (2017) presented combined subgroups with IL2RG/JAK3 (n = 20), RAG 1/2 (n = 13), DCLRE1C (n = 23), IL7R/CD3D (n = 12) and rare/unknown (n = 15).

Appendix 5.2 Multivariable analysis details

Study	Multivariable Model	Outcome Variables	
Antoine 2003[175]	Cox model	Outcome: 3 yr survival after HLA identical transplantation Age at transplantation (mo) ▪ <6 ▪ 6-11 ▪ ≥12 Prophylaxis ▪ Yes ▪ No	Outcome: 3 yr survival after related HLA-mismatched transplantation SCID phenotype ▪ B^+ ▪ B^- Protected environment ▪ Yes ▪ No Pulmonary infection (before transplant) ▪ No ▪ Yes
Gennery 2010[172]	Cox model with stepwise forward selection Analyses adjusted for a centre, comparing centres that transplanted more or less than 50 patients	Outcome: 10 yr survival Years of graft ▪ 2000-2005 ▪ 1995-1999 ▪ <1995 Age at transplantation (mo) ▪ <6 ▪ 6-11 ▪ >12 SCID phenotype ▪ B+ ▪ B- ▪ Other Recipient/donor compatibility ▪ Related genotypically identical ▪ Related phenotypically identical ▪ URD ▪ Related HLA-mismatched	

		Respiratory impairment ▪ No ▪ Yes Septicemia ▪ No ▪ Yes Viral infection ▪ No ▪ Yes T-cell depletion ▪ Yes ▪ No Protected environment ▪ Yes ▪ No Prophylaxis ▪ Yes ▪ No				
Haddad 2018[118]	Cox model with stepwise forward selection	Outcome: Survival in non-MSD HCT Age at HCT (mo) /infection ▪ <3.5/no infection ▪ <3.5/infected/ active ▪ <3.5/infected/ resolved ▪ ≥3.5/infected/ active ▪ ≥ 3.5/infected/ resolved ▪ ≥3.5/no infection	Outcome: Second treatment by HCT, ERT, or GT for patients who initially received non-MSD HCT Age at HCT (mo) /infection ▪ <3.5/no infection ▪ <3.5/infected/ active ▪ <3.5/infected/ resolved ▪ ≥3.5/infected/ active ▪ ≥3.5/infected/ resolved ▪ ≥3.5/no infection	Outcome: GvHD after non-MSD HCT - *aGvHD2-4* Conditioning ▪ No/IS ▪ RIC/MAC Maternal T-cell result ▪ Searched for and absent ▪ ND ▪ Present Stratum ▪ A ▪ B - *c GvHD*	Outcome: T-cell reconstitution 2 to 5 yr after non-MSD HCT Conditioning ▪ No/IS ▪ RIC/MAC Genotype ▪ IL2RG/JAK3 ▪ ADA ▪ DCLRE1C ▪ IL7R, CD3 (any), CD45 ▪ RAG ▪ Other/unknown/ ND Stratum	Outcome: B-cell reconstitution 2 to 5 yr after non-MSD HCT Conditioning ▪ No/IS ▪ RIC/MAC Donor type ▪ MMRD ▪ MUD ▪ URD Genotype ▪ IL2RG/JAK3 ▪ ADA ▪ DCLRE1C ▪ IL7R, CD3 (any), CD45

	Variables considered were phenotypic category, typical SCID (stratum A) vs leaky SCID/Omenn syndrome/reticular dysgenesis (stratum B), age, infection status at HCT, sex, race or ethnic group, maternal T-cell engraftment, genotype, family history, failure to thrive (weight < 5th percentile), donor type, conditioning regimen category (No/IS vs RIC/MAC), graft type, method of graft manipulation, and GvHD prophylaxis approach.	▪ infected/unknown Failure to thrive ▪ No ▪ Yes Genotype ▪ IL2RG/JAK3 ▪ ADA ▪ DCLRE1C ▪ IL7R, CD3 (any), CD45 ▪ Other/unknown/ ND ▪ RAG Race/ethnicity ▪ White and non-Hispanic ▪ American Indian/Alaska native ▪ Black or African American and non-Hispanic ▪ Hispanic ▪ Unknown Stratum ▪ A ▪ B	▪ infected/unknown Conditioning ▪ No/IS ▪ RIC/MAC Decade ▪ 1982-1989 ▪ 1990-1999 ▪ 2000-2012 Donor type ▪ MMRD ▪ MUD ▪ URD Sex ▪ Female ▪ Male Genotype ▪ IL2RG/JAK3 ▪ ADA ▪ DCLRE1C ▪ IL7R, CD3 (any), CD45 ▪ Other/unknown/ND ▪ RAG Stratum ▪ A ▪ B	Donor type/TCD ▪ MMRD-TCD/soybean lectin ▪ MMRD-TCD/CD34 selection ▪ MMRD-other ▪ MUD ▪ URD Maternal T-cell result ▪ Searched for and absent ▪ ND ▪ Present Stratum ▪ A ▪ B	▪ A ▪ B	▪ RAG ▪ Other/unknown/ ND Stratum ▪ A ▪ B
Lankester 2021[136]	Cox model with stepwise forward selection	Outcome: OS SCID group ▪ ADA ▪ IL2Rγ-JAK3-IL7R ▪ RAG-DCLRE1C Pre-HSCT relevant infections ▪ Absent		Outcome: EFS SCID group ▪ ADA ▪ IL2Rγ-JAK3-IL7R ▪ RAG-DCLRE1C Pre-HSCT relevant infections ▪ Absent		

		▪ Present Donor ▪ Matched ▪ MMRD ▪ MMUD Source of hematopoietic stem cells ▪ Bone marrow ▪ Cord blood ▪ Peripheral blood stem cell Transplantation period ▪ 2006-2010 ▪ 2011-2014	▪ Present Donor ▪ Matched ▪ MMRD ▪ MMUD Source of hematopoietic stem cells ▪ Bone marrow ▪ Cord blood ▪ Peripheral blood stem cell
Miyamoto 2021[131]	Cox model with stepwise backward selection	Outcomes: OS after HCT between 2006 and 2016 SCID phenotype ▪ T-B+ SCID ▪ T-B- SCID Age at HCT (mo) ▪ <4 ▪ ≥4 Donor type ▪ MSD ▪ matched UCB (unrelated) ▪ mismatched UCB (unrelated) ▪ ORD ▪ UBM Bacterial or fungal infection at HCT ▪ No ▪ Yes Cytomegalovirus infection prior to HCT ▪ No ▪ Yes Conditioning ▪ fudarabine/busulfan ▪ fudarabine/melphalan ▪ No conditioning/immunosuppression	

		▪ Others		
Pai 2014[121]0	Cox model with stepwise forward selection Variables considered: Age at transplantation, sex, race or ethnic group, maternal engraftment, genotype, B-cell and NK cell phenotypes, family history, infection status, failure to thrive, donor type, use of conditioning, graft type, type of T-cell depletion, and GvHD prophylaxis.	Outcome: Survival at 5 yr Age at transplantation (mo), infection status ▪ 0-3.5 ▪ >3.5, active infection ▪ >3.5, infection resolved ▪ >3.5, no infection Donor type, conditioning regimen ▪ matching sibling donor ▪ mismatched related, no conditioning ▪ mismatched related donor, with conditioning ▪ cord-blood donor ▪ other unrelated or related donor	Outcome: CD3+ T-cell count >1000/mm^3 at 2-5 yr Donor type ▪ matched sibling ▪ mismatched related ▪ other related or unrelated ▪ mismatched related donor versus other unrelated or related donor Conditioning regimen ▪ None or immunosuppression ▪ Reduced intensity or myeloablative conditioning Lymphocyte phenotype ▪ B^+ (versus B^- or B^{low}) ▪ NK^+ (versus NK^- or NK^{low})	Outcome: Independence from IVIG therapy at 2-5 yr Donor type ▪ matched sibling ▪ mismatched related ▪ other related or unrelated ▪ mismatched related donor versus other unrelated or related donor Conditioning regimen ▪ None or immunosuppression ▪ Reduced intensity or myeloablative conditioning

Key: ADA - adenosine deaminase, EFS - event-free survival, GvHD - graft-versus-host disease, HCT - hematopoietic cell transplantation, HLA – human leukocyte antigens, HSCT - hematopoietic stem cell transplantation, IVIG - intravenous immune globulin, IS - immunosuppression, MAC - myeloablative conditioning, mo - months, MSD - matched sibling donor, MMRD - mismatched related donor, MMUD - mismatched unrelated donor, MUD - matched unrelated donor, ND - not determinable, NK - natural killer, ORD - other related donor, OS - overall survival, RIC - reduced-intensity conditioning, SCID - severe combined immunodeficiency, TCD - T-cell depletion, UCB – umbilical cord blood, UBM - unrelated bone marrow, URD - unrelated donor, yr - year

Appendix 6.1 Study model input parameters identified in systematic review of cost effectiveness

Study Country	Parameters – Base Case (Range)
McGhee 2005[193] United States	▪ False negative rate – 1% (0-10%) ▪ False positive rate – 0.4% (0%-10%) ▪ Test cost - $5 (2-$65) ▪ Incidence – 1:50,000 (1:30,000-1:1,000,000) ▪ Treatment cost - $63,116 (20,000-$1,000,000) ▪ Infection treatment cost - $63,116 (0-$1,000,000) ▪ Follow-up cost - $461 (35-$1,000) ▪ IVIG cost - $598,000 (400,000-$900,000) ▪ SCID life expectancy following BMT – 55 yrs (10-77 yrs) ▪ Life expectancy on IVIG – 45 yrs (10-77 yrs) ▪ Probability BMT fails for late transplant – 28% (0-60%) ▪ Probability BMT fails for early transplant – 5% (0-28%) ▪ Probability need IVIG – 65% (50-100%) ▪ Probability missed case – 50 % (0-80%)
Chan 2011[188] United States	▪ Incidence – 1:75,000 (1:25,000-1:500,000) ▪ Screening test performance, sensitivity rate – 0.99 (0.85-1.00) ▪ Screening test performance, specificity rate – 0.99 (0.85-1.00) ▪ Cost, screening test - $4.22 (0.50-$30.00) ▪ Cost, diagnostic test – $250 (50-$1,000) ▪ Cost, HCT late/HCT early – 3 (0.50-10) ▪ Discount rate – 0.03
New Zealand Screening Unit 2014[194] New Zealand	▪ Number of births – 59,431 ▪ SCID incidence – 1:104,215 ▪ Probability, early detection, family history – 0.10 ▪ Probability, early detection, undergoing HSCT – 0.95 ▪ Probability, early detection, successful HSCT – 0.90 ▪ Probability, early detection, unsuccessful HSCT, PTS – 0.10 ▪ Probability, early detection, successful HSCT, no PTS – 0.88 ▪ Probability, early detection, successful HSCT, death – 0.02 ▪ Probability, early detection, unsuccessful HSCT, subsequent HSCT – 0.90

	▪ Probability, early detection, unsuccessful HSCT, successful subsequent HSCT – 0.90 ▪ Probability, early detection, unsuccessful HSCT, unsuccessful subsequent HSCT – 0.10 ▪ Probability, early detection, unsuccessful HSCT, subsequent HSCT, PTS – 0.20 ▪ Probability, early detection, unsuccessful HSCT, successful subsequent HSCT, no PTS – 0.75 ▪ Probability, early detection, successful subsequent HCST, death – 0.05 ▪ Probability, late detection, receiving HSCT – 0.25 ▪ Probability, late detection, successful HSCT – 0.71 ▪ Probability, late detection, successful HSCT, PTS – 0.30 ▪ Probability, late detection, successful HSCT, no PTS – 0.60 ▪ Probability, late detection, unsuccessful HSCT, subsequent HSCT – 0.90 ▪ Probability, late detection, unsuccessful HCST, successful subsequent HSCT – 0.67 ▪ Probability, late detection, unsuccessful HCST, subsequent HSCT, PTS – 0.40 ▪ Probability, late detection, unsuccessful HCST, subsequent HSCT, no PTS – 0.50 ▪ Probability, early detection, test sensitivity – 0.999 ▪ Probability, early detection, test specificity – 0.996 ▪ Probability, number of positive tests that require a second TREC test – 0.920 ▪ Probability, number of positive tests that require flow cytometry – 0.180 ▪ Costs, early detection, HSCT - $70,194 ▪ Costs, late detection, excluding HSCT - $141,271 ▪ Costs, late detection, including HSCT - $254,938 ▪ Costs, late detection, additional HSCT - $157,435 ▪ Costs, post-HSCT support, specialist follow-up, no PTS - $6,854 (discounted NPV: $6,615) ▪ Costs, post-HSCT support, early detection - $39,838 (discounted NPV: $1,032,664) ▪ Costs, post-HSCT support, late detection - $39,838 (discounted NPV: $830,986) ▪ Costs, initial screening costs per screen, $5.22 ▪ Costs, confirmatory screening costs per test - $369 ▪ Costs, first HSCT donor procurement - $45,000 ▪ Costs, early detection, post-HSCT cost of dying, life-years 2 to 10 - $38,584 ▪ Costs, late detection, post-HSCT cost of dying, life-years 2 to 10 - $68,456 ▪ Post treatment period, early detection, length of treatment – lifetime ▪ Post treatment period, late detection, length of treatment – lifetime ▪ Subsequent treatment, number of additional HSCT – 1 ▪ Survival years, early detection, successful HSCT, no PTS – 60.8 (discounted NPV – 25.92) ▪ Survival years, early detection, successful HSCT, PTS – 71.5 (discounted NPV – 27.05)

	▪ Survival years, late detection, successful HSCT, no PTS – 35.5 (discounted NPV – 20.86) ▪ Survival years, late detection, successful HSCT, PTS – 41.8 (discounted NPV – 22.55) ▪ Survival years, early detection, unsuccessful HSCT – 1.44 (discounted NPV – 1.43) ▪ Survival years, late detection, unsuccessful HSCT – 1.44 (discounted NPV – 1.43) ▪ Survival years, early detection, no HSCT – 1.00 ▪ Survival years, late detection, no HSCT – 1.00
The Institute of Health Economics 2016[192] Alberta (Canada)*	▪ Incidence – 1:58,000 (1:100,000-2:58,000) ▪ Incidence of syndromes with T-cell impairment, secondary T-cell impairment, and variant SCID – 1:11,434 ▪ Proportion, with screening and early detection, sequelae – 0% ▪ Mortality rate, with screening and early detection – 8.16% (6.53-9.80%) ▪ Proportion, without screening and delayed detection, sequelae – 100% ▪ Mortality rate, without screening and delayed detection – 72.73% (58.15-87.27%) ▪ Time elapsed before diagnosis, without screening and delayed detection – 3 months ▪ Incremental cost of adding SCID screen to current programme – 15.02$ ▪ Flow cytometry confirmation, blood count, and genetic confirmation -$4,892 ▪ Treatment for sequelae (early treatment), hospitalisation, HSCT, one time - $81,818.59 ▪ Treatment for sequelae (early treatment), physician, HSCT, one time – $6,545.49 ▪ Treatment for sequelae (early treatment), hospitalisation, post-treatment management, one time – $39,569.83 ▪ Treatment for sequelae (early treatment), physician, post-transplant management, one time - $3,165.59 ▪ Treatment for sequelae (late treatment), hospitalisation, HSCT, one time - $245,455.77 ▪ Treatment for sequelae (late treatment), physician, HSCT, one time – $6,545.49 ▪ Treatment for sequelae (late treatment), hospitalisation, post-treatment management, one time – $118,709.49 ▪ Treatment for sequelae (late treatment), physician, post-transplant management, one time - $9,496.79 ▪ Condition management, initial physician consultation, per visit - $346.00 ▪ Condition management, follow-up physician consultation, per visit - $123.60 ▪ Condition management, genetic counselling, one time - $266.37 ▪ Test sensitivity – 0.99 ▪ Test specificity – 0.99
Ding 2016[190] Washington (United States)	▪ Birth prevalence of SCID – 1:58,000 (1:46,000:1:80,000) ▪ Proportion of SCID cases detected without NBS – 0.203 ▪ Birth prevalence of non-SCID TCL – 1:14:000 (1:11,600-1:16,400) ▪ Sensitivity of the overall screen process – 99.50% (99.00-100.00%) ▪ Specificity of the overall screen process – 99.97% (99.92-99.98%) ▪ Survival rate, early-identified SCID (pre-treatment) – 94%

	▪ Survival rate, early-identified SCID (post-treatment) – 94% ▪ Survival rate, late-identified SCID (pre-treatment) – 78% ▪ Survival rate, late-identified SCID (post-treatment) – 69% ▪ Survival rate, cumulative survival for early-identified SCID – 88% (85-94%) ▪ Survival rate, cumulative survival for late-identified SCID – 54% (38-72%) ▪ Costs, screening and diagnosis, lab test for TREC assay per sample - $4.04 (3.00-$6.00) ▪ Costs, screening and diagnosis, short-term follow-up per positive case - $50.00 ▪ Costs, screening and diagnosis, flow cytometry per baby - $250.00 ▪ Costs, screening and diagnosis, additional costs for transient TCL - $2,360 ▪ Costs, screening and diagnosis, additional costs for idiopathic TCL - $6,000 ▪ Costs, screening and diagnosis, additional costs for other non-SCID TCL - $6,000 ▪ Costs, treatment, Average cost per infant with SCID who die before definitive treatment - $300,000 ▪ Costs, treatment, Average cost per infant with ADA SCID who do not undergo early HCT - $450,000 (200,000-$750,000) ▪ Costs, treatment, Average costs for infants with SCID who receive HSCT as first-line therapy, early identified baby - $100,000 (80,000-$120,000) ▪ Costs, treatment, Average costs for infants with SCID who receive HSCT as first-line therapy, late identified baby - $450,000 (300,000-$1,200,000) ▪ VSL - $ 9,000,000 (alterative $4,200,000)
The National Board of Health and Welfare 2019[198] Sweden	▪ Number of births per year - 116,000 ▪ Incidence - 1:50,000 (1:20,000 – 1:37,000) ▪ Time horizon - 0 to 90 years (max) ▪ Known family history - 28% ▪ Survival, 1 year, early HSCT - 0.94 ▪ Survival, 1 year, late HSCT - 0.79 ▪ Survival, 5 year, late HSCT - 0.94 ▪ Survival, 5 year, late HSCT - 0.69 ▪ Annual risk of death >5 years - constantly elevated risk as well as the population's age-adjusted risk of death (hazard ratio 6.09) (1.5 in sensitivity analysis) ▪ Clinical factors, proportion of retests - 5% ▪ Clinical factors, Proportion tested in national screening - 99.5% ▪ Clinical factors, The sensitivity of the screening test - 100% ▪ Clinical factors, Distribution at current position, early HSCT - 28% ▪ Clinical factors, Distribution at current position, late HSCT - 63% ▪ Clinical factors, Distribution at screening, early HSCT - 100% ▪ Clinical factors, Distribution at screening, late HSCT - 0% ▪ Quality of life, 0-17 yrs, early HSCT - 0.96 ▪ Quality of life, 0-17 yrs, late HSCT - 0.82

	▪ Quality of life, 18 years plus - average of Swedish population while maintaining relative diff between early versus late ▪ Medical expenses, screening, testing of blood - SEK 60 (54 to 80) ▪ Medical expenses, cost per examination, blood flow, and test cytometry - SEK 1,640 ▪ Medical expenses, before transplant, total, early HSCT - SEK 1,064,729 ▪ Medical expenses, before transplant, total, late HSCT - SEK 1,671,248 ▪ Medical expenses, after transplant, total, early HSCT - SEK 2,024,381 ▪ Medical expenses, after transplant, total, late HSCT - SEK 2,664,531 ▪ Medical expenses, Follow-up, team visit paediatric medicine (5 – 17 years) - SEK 8,904 ▪ Medical expenses, Follow-up, visits to doctors and nurses for infectious disease medicine (>17 years) - SEK 2,869 ▪ Medical expenses, Annual number of follow-up appointments, early HSCT – 4 (2-6) ▪ Medical expenses, Annual number of follow-up appointments, early HSCT – 10 (6-12) ▪ Medical expenses, Annual cost of drugs, early HSCT - SEK 23,618 ▪ Medical expenses, Annual cost of drugs, late HSCT - SEK 31,086 ▪ Loss of production, Expected lost production value per day - SEK 1,258 ▪ Loss of production, Isolation for infection protection reasons, early HSCT - 90 days ▪ Loss of production, Isolation for infection protection reasons, late HSCT - 180 days ▪ Loss of production, Care days in the hospital before stem cell transplantation, care of children, early HSCT - 40 days ▪ Loss of production, Care days in the hospital before stem cell transplantation, care of children, late HSCT - 68 days ▪ Loss of production, Care days in the hospital after stem cell transplantation, care of children, early HSCT - 68 days ▪ Loss of production, Care days in the hospital after stem cell transplantation, care of children, late HSCT - 92 days		
Bessey 2019[(101)]** United Kingdom	▪ Number of births (UK) - 780,835 ▪ Incidence of SCID - 1:49,000 (1:39,857-1:61,527) ▪ Incidence of undiagnosed - SCID 1:521,000 (1:167,052-1:7,236,800) ▪ Incidence of syndromes - 1:45,000 (1:24,390-1:110,606) ▪ Incidence of secondary conditions - 1:130,000	▪ Cost, screening, Band 5 worker (50% FTE) - £12,744 ▪ Cost, screening, workstation - £2,700 ▪ Cost, screening, screening test per baby - £3.50 ▪ Cost, Presumptive cases, flow cytometry - £25 ▪ Cost, Presumptive cases, 1 immunology appointment - £251 ▪ Cost, Presumptive cases, total - £276 ▪ Cost, Follow up preterm & secondary to other conditions, 2 immunology appointment - £503 ▪ Cost, Follow up preterm & secondary to other conditions, 2x flow cytometry - £50 ▪ Cost, Follow up preterm & secondary to other conditions – £553 ▪ Cost, Syndromes 4 year follow-up, 2x	▪ Long term outcome parameters ▪ Requires immunoglobin, Early Diagnosed - 0.25 ▪ Requires immunosuppressive drugs (steroids), Early Diagnosed - 0.056 ▪ Considered health, Early Diagnosed - 0.88 ▪ Considered healthy , Late Diagnosed - 0.85 ▪ No problems, Early Diagnosed - 0.49 ▪ No problems, Late Diagnosed - 0.29 ▪ Requires standing antibiotics , Early Diagnosed - 0.25 ▪ Requires standing antibiotics ,

	(1:50,686-1:782,506) ▪ Incidence of idiopathic TCL - 1:99,000 (1:42,255-1:432,482) ▪ Incidence of positive TREC in pre-terms - 1:99,000 (1:42,255-1:432,482) ▪ Presumptive positives, 20 copies/µL - 0.041% (0.0035-0.1018%) ▪ Sensitivity for SCID - 0.99 (0.985-0.998) ▪ Proportion of SCID patients with a family history - 0.30 (0.21-0.41) ▪ Proportion of SCID that is ADA-SCID - 0.17 (0.1-0.26) ▪ Proportion of SCID patients with a matched family donor available - 0.25 (0.07-0.5) ▪ Pre HSCT mortality, late diagnosed - 35.3% (22.8-49.3%) ▪ Pre HSCT mortality, early diagnosed - 1.68% (0.11-7.63%)	multispecialty appointments per year - £2,011 ▪ Cost, Syndromes 4 year follow-up, 2x flow cytometry test per year – £50 ▪ Cost, Syndromes 4 year follow-up, total 4 years (undiscounted) - £754 ▪ Cost, Syndromes 4 year follow-up, total 4 years (discounted) - £4,872 ▪ Costs, Idiopathic SCID 0-2 years 2x immunology appointments per year - £754 ▪ Costs, Idiopathic SCID 2-5 years, 3x immunology appointments per year - £503 ▪ Costs, Idiopathic SCID (IG and antibiotics), Immunoglobulin 1st year – £1,789 ▪ Costs, Idiopathic SCID (IG and antibiotics), Immunoglobulin 2nd year – £2,716 ▪ Costs, Idiopathic SCID (IG and antibiotics), Immunoglobulin 3rd year – £3,319 ▪ Costs, Idiopathic SCID (IG and antibiotics), Immunoglobulin 4th year – £3,875 ▪ Costs, Idiopathic SCID (IG and antibiotics), Immunoglobulin 5th year - £4,253 ▪ Costs, Idiopathic SCID (IG and antibiotics), Antibiotics 1st year – £310 ▪ Costs, Idiopathic SCID (IG and antibiotics), Antibiotics 2nd year – £620 ▪ Costs, Idiopathic SCID (IG and antibiotics), Antibiotics 3rd year – £620 ▪ Costs, Idiopathic SCID (IG and antibiotics), Antibiotics 4th year – £620 ▪ Costs, Idiopathic SCID (IG and antibiotics), Antibiotics 5th year - £620 ▪ Costs, Idiopathic SCID (IG and antibiotics), total 5 years (undiscounted) - £21,757 ▪ Costs, Idiopathic SCID (IG and antibiotics),	Late Diagnosed - 0.29 ▪ Persistent rashes, Early Diagnosed - 0.23 ▪ Persistent rashes, Late Diagnosed - 0.29 ▪ ADHD , Early Diagnosed - 0.16 ▪ ADHD , Late Diagnosed - 0.17 ▪ Diarrhoea, Early Diagnosed - 0.05 ▪ Diarrhoea, Late Diagnosed - 0.19 ▪ Height <3rd percentile , Early Diagnosed - 0.05 ▪ Height <3rd percentile , Late Diagnosed - 0.17 ▪ Weight <3rd percentile , Early Diagnosed - 0.02 ▪ Weight <3rd percentile , Late Diagnosed - 0.17 ▪ Warts, Early Diagnosed - 0.11 ▪ Warts, Late Diagnosed - 0.16 ▪ Asthma, Early Diagnosed - 0.15 ▪ Asthma, Late Diagnosed - 0.16 ▪ Developmental delay , Early Diagnosed - 0.05 ▪ Developmental delay , Late Diagnosed - 0.18 ▪ GERD, Early Diagnosed - 0.05 ▪ GERD, Late Diagnosed - 0.04 ▪ Oral aversion, Early Diagnosed - 0.02 ▪ Oral aversion, Late Diagnosed - 0.04 ▪ Hyperthyroidism, Early

	▪ Pre HSCT mortality odds ratio (early diagnosed) – 0.03 ▪ HSCT mortality, late diagnosed - 38.7% (22.4-56.3%) ▪ HSCT mortality, early diagnosed - 8.48% (1.79-23.4%) ▪ HSCT mortality odds ratio (early diagnosed) – 0.15 ▪ ADA-SCID pre HSCT morality (late diagnosed) - 0.21 ▪ ADA-SCID pre HSCT mortality odds ratio (early diagnosed) – 0.06 ▪ ADA-SCID HSCT mortality (matched family donor) (late diagnosed) - 0.33 ▪ ADA-SCID HSCT mortality odds ratio (matched family donor) (early diagnosed) – 0.11 ▪ ADA-SCID Gene therapy mortality – 0.05 ▪ Number of days HSCT - 54.0 ▪ Early diagnosis, total	total 5 years (discounted) - £20,142 ▪ Costs, Diagnosis SCID, 1x immunology appointment - £251 ▪ Costs, Diagnosis SCID, 1x genetic test - £567.5 ▪ Costs, Diagnosis SCID total - £711 ▪ Costs, Diagnosis idiopathic SCID, 1x immunology appointment - £251 ▪ Costs, Diagnosis idiopathic SCID, 1x genetic test (206 exome panel) - £1,300 ▪ Costs, Diagnosis syndromes, total - £1,551 ▪ Costs, Diagnosis syndromes, 1x immunology appointment - £251 ▪ Costs, Diagnosis syndromes, 50% 1x genetic test (206 exome panel) - £1,300 ▪ Costs, Diagnosis syndromes, total - £1,551 ▪ Costs, Enzyme replacement therapy (Adagen), 1 vial per week - £7,500 ▪ Costs, Enzyme replacement therapy (Adagen), administration, 1x non-clinical immunology appointment per week - £180 ▪ Costs, Enzyme replacement therapy (Adagen), early diagnosis 11 weeks - £84,475 ▪ Costs, Enzyme replacement therapy (Adagen), late diagnosis 26 weeks - £199, 668 ▪ Costs, Inpatient care, Day cost inpatient paediatric disorder of the immunity (average) - £1,495 ▪ Costs, Inpatient care, Day cost inpatient paediatric critical care level 3 - £1,967 ▪ Costs, HSCT, cost of HSCT 54 days - £80,556 ▪ Costs, HSCT, Early diagnosed HSCT – HSCT + 29 days non-critical care + 2.6 days critical	Diagnosed - 0.03 ▪ Hyperthyroidism, Late Diagnosed - 0.01 ▪ Seizure disorder, Early Diagnosed - 0.02 ▪ Seizure disorder, Late Diagnosed - 0.01 ▪ GVHD - 0.04 ▪ Cerebral palsy - 0.02 ▪ Autoimmune disease - 0.02

	days non-critical care - 82.6 (50.3-122.8) ▪ Early diagnosis, total days critical care - 3.96 (0.15-8.41) ▪ Late diagnosis, total days non-critical care - 144 (108.6-184.3) ▪ Late diagnosis, total days critical care - 8.19 (3.72-14.4) ▪ Early diagnosis - Gene therapy - Total non-critical care preGT – 12.25 (7.8-17.7) ▪ Early diagnosis - Gene therapy - Total critical care preGT – 0.25 (0.03, 0.7) ▪ Late diagnosis - Gene therapy - Total non-critical care preGT – 45.7 (35.6-57.1) ▪ Late diagnosis - Gene therapy - Total critical care preGT – 4.37 (1.59,8.53) ▪ QALYs, early diagnosis, 1979–2015 cohort - 0.95	care - £128,363 ▪ Costs, HSCT, Late diagnosed HSCT – HSCT + 90 days non-critical care + 3.8 days critical care - £231,186 ▪ Costs, gene therapy, cost of Strimvelis - £509,027 ▪ Costs, gene therapy, Early diagnosed GT – GT + 12 days non-critical care + 0.25 days critical care - £527,829 ▪ Costs, gene therapy, Late diagnosed GT – GT + 45 days non-critical care + 3.3 days critical care - £585,994 ▪ Costs, Death before transplant 12.5 days non-critical care + 12.5 days critical care - £43,368 ▪ Costs, Follow-up SCID well 1st year, 4x immunology appointments per year – £1,005 ▪ Costs, Follow-up SCID well 2nd-3rd year, 2x immunology appointments per year - £503 ▪ Costs, Follow-up SCID well 4th year, 1x immunology appointments per year - £251 ▪ Costs, Follow-up SCID not well 1st year, 6x immunology appointments per year -£1,508 ▪ Costs, Follow-up SCID not well 2nd-3rd year, 4x immunology appointments per year - £1,005 ▪ Costs, Follow-up SCID not well 4th year, 2x immunology appointments per year - £503 ▪ Costs, Follow-up SCID not well 5th year, 1x immunology appointments per year - £251 ▪ Costs, SCID enteral feeding, Gastrostomy surgery - £1,539 ▪ Costs, SCID enteral feeding, 6 x dietician appointments (per year) - £496	

	▪ QALYs, late diagnosis, 1979–2015 cohort - 0.82 ▪ QALYs, early diagnosis, 2000–2015 cohort - 0.96 ▪ QALYs, late diagnosis, 2000–2015 cohort - 0.87 ▪ Cost HSCT (early diagnosed) - £128,363 ▪ Cost HSCT (late diagnosed) - £231,186 ▪ Cost death prior to HSCT - £43,368 ▪ Presumptive positive cost - £276 ▪ Diagnosis SCID - £711 ▪ Diagnosis idiopathic SCID and syndromes - £1,551 ▪ Idiopathic SCID follow-up, 5 years discounted - £20,142 ▪ Syndromes 4 year follow-up - £4,872 ▪ Follow-up preterm & secondary to other conditions - £533	▪ Costs, SCID enteral feeding, Feeds 1st year (50% calorific requirements) - £1,315 ▪ Costs, SCID enteral feeding, Feeds 2nd year (50% calorific requirements) - £1,996 ▪ Costs, SCID Mild development delay, 0-3 years - £1,404 ▪ Costs, SCID Mild development delay, 4-11 years - £24,138 ▪ Costs, SCID Mild development delay, 12-17 years - £24,138 ▪ Costs, SCID Mild development delay, 18+ years - £9,347 ▪ Costs, IG, For whole life (cost increases with age up to 18 years) - £1,789-£16,481 ▪ Costs, Antibiotics, 1st year per year (125 mg per day, oral solution) - £310 ▪ Costs, Antibiotics,2nd-5th year per year (250 mg per day, oral solution) - £620 ▪ Costs, Antibiotics,6th year+ per year (250 mg per day, oral solution) - £28 ▪ Costs, Steroids (2 years), 2mg/kg/day - £772-£943 ▪ Costs, ADHD (5-18 years), Medication per year - £295 ▪ Costs, ADHD (5-18 years), 2x CAHMs appointments per year - £599	
van der Ploeg 2019[197] Netherlands	▪ Incidence of SCID – 1:58,000 (1:46,000-1:80,000) ▪ SCID patients early detected without neonatal screening – 20% (15-30%)		

	▪ Incidence of non-SCID – 1:14,000 (1:8,200-1:16,400) ▪ Non-SCID patients detected without neonatal screening – 100% (0%) ▪ Probability, survive until treatment when SCID is detected early – 94% (92-98%) ▪ Probability, survive after treatment when SCID is detected early – 92% (90-98%) ▪ Probability, survive until treatment when SCID is detected late – 78% (65-80%) ▪ Probability, survive after treatment when SCID is detected late – 80% (61-90%) ▪ Health status after transplantation, early/late detection, good – 80%/50% (70%/50%) ▪ Health status after transplantation, early/late detection, moderate – 15%/30% (20%/30%) ▪ Health status after transplantation, early/late detection, poor - 5%/20% (10%/20%) ▪ Life expectancy after transplantation, dependent on health status, good – 65 yrs (discounted 40.8 yrs) ▪ Life expectancy after transplantation, dependent on health status, moderate – 40 yrs (discounted 30.3 yrs) ▪ Life expectancy after transplantation, dependent on health status, poor – 25 yrs (discounted 21.4 yrs) ▪ Quality of life, adjusted, utility, good – 0.95 (0.75-1.0) ▪ Quality of life, adjusted, utility, moderate – 0.75 (0.5-0.95) ▪ Quality of life, adjusted, utility, poor – 0.5 (0.3-0.7) ▪ Number of children without SCID who get flow cytometry (plus visit to clinic) because of suspected SCID - 10/child with SCID without screening ▪ Retest on same sample at < 25 TREC/µl - 0.39% (0.1-0.6%) ▪ Second heel prick – 0.25% (0.08-0.41%) ▪ Children with flow cytometry in total screened population – 0.08% (0.01-0.14%) ▪ Sensitivity total screening program, SCID – 100% (99%) ▪ Sensitivity total screening program, non-SCID – 100% ▪ Distribution non-SCID – 7.1% transient, 2.9% idiopathic, and 90.0% other non-SCID ▪ Costs, screening test, TREC within NBS program, - €4.71 (€4.36 + devices €0.35) (3.50-€5.50) ▪ Costs, retest, duplo - €9.42 (7-€11) ▪ Costs, second heel prick - €29.01 (blood collection €20.30 + postage €1.60 + processing €2.40 + TREC test) ▪ Costs, diagnostics for referred children - € 1,598 (paediatrician €102), flow cytometry (€498 including clinic visit), repeat flow cytometry for 2/3 of screen positives, genetic tests of €2,000 for 1/3 ▪ Costs, diagnostics in situation without screening for children with SCID or non-SCID - € 2,600 per child with SCID or non-SCID (paediatrician €102), flow cytometry (€498 including clinic visit), genetic tests (€,2000) ▪ Costs, transplantation SCID when detected early - €90,000 (75,000–€125,000) ▪ Costs, transplantation SCID when detected late - €205,000 (150,000–€450,000) ▪ Costs, treatment non-SCID, transient - €2,200 (1,500-€3,000) ▪ Costs, treatment non-SCID, idiopathic - €6,200 (4,000-€$8,000)

	▪ Costs, treatment non-SCID, other - €6,200 (4,000-€$8,000) ▪ Costs, treatment for child with SCID which dies before transplantation - €135,000 (75,000-€225,000) ▪ Costs, treatment in remaining lifetime, dependent on health status (per year), good - €26 ▪ Costs, treatment in remaining lifetime, dependent on health status (per year), moderate - €18,148 ▪ Costs, treatment in remaining lifetime, dependent on health status (per year), poor - €9,713 ▪ Costs, end of life (per year, during last 5 years), good - €0 ▪ Costs, end of life (per year, during last 5 years), moderate or poor - €6,314 because of lung disease/malignant ▪ Productivity costs (additional sickness leave for SCID in comparison to general population), good - €0 ▪ Productivity costs (additional sickness leave for SCID in comparison to general population), moderate - €4,208*25% ▪ Productivity costs (additional sickness leave for SCID in comparison to general population), poor - €0
Palko 2020[191] Finland	▪ birth rate - 56 241 (47,577-60,980) ▪ Incidence of SCID - 1:58,000 (1:80,000-1:46,000) ▪ % Of SCID patients with a family history of SCID - 13.3% (5%-20%) ▪ Lymphopenias other than Incidence of SCID - 1:14,000 (1:16,400 - 1:8,200) ▪ % of other lymphopenias detected without screening - 50% (0%-100%) ▪ Likely to be alive to start treatment if SCID is detected in time - 98% (maximum 99%) ▪ Likelihood of survival after treatment if SCID is detected in a timely manner - 92% (maximum 95%) ▪ Likely to be alive to start treatment if the SCID is not detected in time - 65% (maximum 73%) ▪ Likelihood of survival after treatment if SCID is not detected in a timely manner - 61% (maximum 68%) ▪ Health status after stem cell transplantation. found in time / found late, good: 80%/50% ▪ Health status after stem cell transplantation. found in time / found late, average: 15%/30% ▪ Health status after stem cell transplantation. found in time / found late, weak: 5%/20% ▪ Life expectancy after stem cell transplantation (depending on health status), good - 65 yrs ▪ Life expectancy after stem cell transplantation (depending on health status), average - 40 yrs ▪ Life expectancy after stem cell transplantation (depending on health status), weak - 25 years ▪ Extra number of flow cytometries per SCID (without screening) - 25 (10-100) ▪ The first screening test % <TREC limit value - 0.08% (0.02%-0.23%) ▪ % second heel blood sample - 0.25% ▪ Sensitivity of screening - 100% ▪ Non-SCID shares: 15% transient, 19% idiopathic, 66% other ▪ cost Screening test (as part of the screening for neonatal metabolic diseases) - 4 € (0€-6€) ▪ cost, retest - 4 € (0€-6€) ▪ cost, repeat sample - 18.21€ ▪ cost, children who receive a referral diagnostic -1,043€

	▪ cost, Diagnostic costs without SCID screening (paediatric visit, flow cytometry, genetic test) - 1,565€ ▪ cost, The cost of stem cell transplantation when SCID is detected in a timely manner - 88,961€ ▪ cost, cost of stem cell transplantation when the SCID is detected late - 202,096€ ▪ cost, operation costs other than SCID - transient 744€, idiopathic 1,325€, others 1,325€ ▪ cost, treatment SCID for a patient who dies before transplantation - 177,922€ ▪ cost, treatment costs/year during life, depending on health condition, good - 26.5€ ▪ cost, treatment costs/year during life, depending on health condition, average - 17,649 € ▪ cost, treatment costs/year during life, depending on health condition, weak – 9,453€ ▪ cost, for the last five years of life/year - 1,762€		
SESCS 2020[195]*** Spain	▪ Number of births in Spain – 372,777 (n/a) ▪ SCID incidence - 1:50,000 (Beta (1; 49,999)) AND 1:60,000 (Beta (1;59,999)) ▪ Incidence of undiagnosed SCID - 1:521,000 (Beta (1,5; 780,833)) ▪ Sensitivity of the screening test for IDCG - 0.99 (Beta (1567.17; 15.83)) ▪ Incidence of syndromes - 1:32,500 (Beta (4; 130,000)) ▪ Incidence of secondary diseases - 1:130,000 (Beta (1; 130,000)) ▪ Incidence of idiopathic T-cell lymphopenia - 1:65,000 (Beta (2; 130,000)) ▪ Incidence of positive screening test results in preterm births (including FP) - 1:130,000 (Beta (1; 130,000)) ▪ Presumptive positive cases (FP + premature) (20 copies/ul) - 1:14,500 (Beta (9;130,000)) ▪ Proportion of variants and syndromes not diagnosed at birth – 0.33 (Beta (7; 14))	▪ Long term outcome parameters ▪ Requires immunoglobin - 0.25 ▪ Requires immunosuppressive drugs (steroids) - 0.056 ▪ Considered health, Early Diagnosed - 0.88 ▪ Considered healthy , Late Diagnosed - 0.85 ▪ No problems, Early Diagnosed - 0.49 ▪ No problems, Late Diagnosed - 0.29 ▪ Requires standing antibiotics , Early Diagnosed - 0.25 ▪ Requires standing antibiotics , Late Diagnosed - 0.29 ▪ Persistent rashes, Early Diagnosed - 0.23 ▪ Persistent rashes, Late Diagnosed - 0.29	▪ Estimated use of resources and aggregate costs ▪ Presumptive positive cases, Flow cytometry - 351.69€ ▪ Presumptive positive cases, Proliferation study lymphocyte - 67.28 € ▪ Presumptive positive cases, Specialist visit - 147.00 € ▪ Presumptive positive cases, Total - 565.97 € ▪ IDCG diagnosis, Specialist visit - 147.00 € ▪ IDCG diagnosis, genetic test - 650.00 € ▪ IDCG diagnosis, total - 797.00 € ▪ Variant Diagnosis, Specialist visit - 147.00 € ▪ Variant Diagnosis, genetic test - 650.00 € ▪ Variant Diagnosis, total - 797.00 € ▪ Syndrome diagnosis, Specialist visit - 147.00 € ▪ Syndrome diagnosis, genetic test - 650.00 €

	▪ Proportion of SCID patients with a family history - 0.18 (Beta (9; 41)) ▪ SCID-ADA ratio – 0.17 (Beta (14; 82)) ▪ Proportion of compatible sibling donors over available compatible family donors for SCID type ADA (1st receive gene therapy) – 0.25 (Beta (3.5,10.5)) ▪ Mortality before HSCT (late diagnosis) – 0.35 (Beta (31; 17)) ▪ OR mortality before HSCT (early diagnosis) – 0.03 (Lognormal (-4.03; 1.05)) ▪ Mortality after HSCT (late diagnosis) – 0.39 (Beta (19; 12)) ▪ OR mortality after HSCT (early diagnosis) – 0.15 (Lognormal (-2.1; 0.6)) ▪ Mortality before HSCT (late diagnosis) in patients with SCID-ADA – 0.21 (Beta (38, 10)) ▪ OR mortality before HSCT (early diagnosis) in patients with SCID-ADA – 0.06 (Lognormal (-3.31; ,1.07)) ▪ Mortality after HSCT in SCID patients ADA (matched family donor) (late diagnosis) – 0.33 (Beta (8; 4)) ▪ OR mortality after HSCT in patients SCID-ADA (matched family donor) (early diagnosis) – 0.11 (Lognormal (-2.91; 1.2)) ▪ Mortality after gene therapy in patients with SCID-ADA – 0.05 (Beta (18; 1)	▪ ADHD , Early Diagnosed - 0.16 ▪ ADHD , Late Diagnosed - 0.17 ▪ Diarrhoea, Early Diagnosed - 0.05 ▪ Diarrhoea, Late Diagnosed - 0.19 ▪ Height <3rd percentile , Early Diagnosed - 0.05 ▪ Height <3rd percentile , Late Diagnosed - 0.17 ▪ Weight <3rd percentile , Early Diagnosed - 0.02 ▪ Weight <3rd percentile , Late Diagnosed - 0.17 ▪ Warts, Early Diagnosed - 0.11 ▪ Warts, Late Diagnosed - 0.16 ▪ Asthma, Early Diagnosed - 0.15 ▪ Asthma, Late Diagnosed - 0.16 ▪ Developmental delay , Early Diagnosed - 0.05 ▪ Developmental delay , Late Diagnosed - 0.18 ▪ GERD, Early Diagnosed - 0.05 ▪ GERD, Late Diagnosed - 0.04	▪ Syndrome diagnosis, total - 797.00 € ▪ Follow-up of others secondary diseases, specialist visit (2) - 294.00 € ▪ Follow-up of others secondary diseases, flow cytometry (2) - 703.38 € ▪ Follow-up of others secondary diseases, total - 997.38 € ▪ Syndromic follow-up during four years, visit to experts (8) – 1,176.00 € ▪ Syndromic follow-up during four years - 703.38 € ▪ Syndromic follow-up during four years – 1,879.38 € ▪ variant SCID, 0-2 years, Specialist visit (3) - 441.00 € ▪ variant SCID, 2-5 years, Specialist visit (2) - 294.00 € ▪ variant SCID, 0-5 years, Immunoglobulins first year – 1,258.60 € ▪ variant SCID, 0-5 years, Immunoglobulins second year – 2,062.85 € ▪ variant SCID, 0-5 years, Immunoglobulins third year – 2,595.53 € ▪ variant SCID, 0-5 years, Immunoglobulins fourth year – 3,022.73 € ▪ variant SCID, 0-5 years, Immunoglobulins fifth year –

	▪ Number of days of hospital stay after HSCT – 54.0 (n/a) ▪ Days in non-critical care, early diagnosis – 82.6 (Gamma (19.73; 4.19)) ▪ Days in critical care, early diagnosis – 3.96 (Gamma (1.35; 1.92)) ▪ Days in non-critical care, late diagnosis - 144 (Gamma (55.39; 2.6)) ▪ Days in critical care, late diagnosis – 8.19 (Gamma (8.9; 0.92)) ▪ Days in non-critical care before gene therapy, early diagnosis -12.25 (Gamma (22.97; 0.53)) ▪ Days in critical care before gene therapy, early diagnosis - 0.25 (Gamma (1.94; 0.13)) ▪ Days in non-critical care before gene therapy, late diagnosis – 45.7 - Gamma (69.72; 0.66) ▪ Days in critical care before gene therapy, late diagnosis – 4.37 (Gamma (5.93; 0.74)) ▪ TREC screening test (PerkinElmer) by determination - 4 €, 5 €, 6 € ▪ Flow cytometry – 351.69 € ▪ Lymphocyte proliferation study – 67.28 € ▪ Genetic testing (mass sequencing of 323 genes) - 650 € ▪ Annual salary cost of a technician laboratory – 25,494 € ▪ PCR Workstation/UV Cabinet – 6,000 € ▪ Allogeneic bone marrow transplant –	▪ Oral aversion, Early Diagnosed - 0.02 ▪ Oral aversion, Late Diagnosed - 0.04 ▪ Hyperthyroidism, Early Diagnosed - 0.03 ▪ Hyperthyroidism, Late Diagnosed - 0.01 ▪ Seizure disorder, Early Diagnosed - 0.02 ▪ Seizure disorder, Late Diagnosed - 0.01 ▪ GVHD - 0.04 ▪ Cerebral palsy - 0.02 ▪ Autoimmune disease - 0.02	3,393.52 € ▪ variant SCID, 0-5 years, Antibiotics first year - 15.20 € ▪ variant SCID, 0-5 years, Second to fifth year antibiotics - 30.40 € ▪ SCID tracking in patients who are NOT feel good during, first year (6) - 882.00 € ▪ SCID tracking in patients who are NOT feel good during, second year (4) - 588.00 € ▪ SCID tracking in patients who are NOT feel good during, third-fourth year (2) - 294.00 € ▪ SCID tracking in patients who are NOT feel good during, fifth year and successive years - 147.00 € ▪ SCID tracking in patients who feel good during, first year (4) - 588.00€ ▪ SCID tracking in patients who feel good during, second-third year (2) - 294.00€ ▪ SCID tracking in patients who feel good during fourth and successive years - 147.00€ ▪ SCID - enteral feeding, Surgery for gastrostomy – 1,549.00€ ▪ SCID - enteral feeding, Visit to paediatrician (consultation nutrition) (6) – 882.00€

	75,150 € ▪ Utility in the case of early diagnosis - 0.95 (Beta(212.39; 6.62), SD 0.09) ▪ Utility in the case of late diagnosis - 0.82 (Beta(165.35, 21.89), SD 0.25) ▪ Day of medical stay in the unit immunodeficienies – 1,186 € ▪ Pediatric intensive care – 2,365 € ▪ Enzyme replacement therapy (Revcovi®), a vial – 7,500 € ▪ Gene therapy (Strimvelis®) – 594,000 € ▪ Percutaneous gastrostomy fluoroscopy – 1,549 € ▪ Consultation with a specialist in the Unit Immunodeficiencies (subsequent consultation hi-tech hospital) - 147 € ▪ Specialized care services people with mental retardation - 117 € ▪ Mild disability, all age groups (annual costs) – 1,917 € ▪ Steroid-sparing immunosuppressants (capsules), cost per mg – 0.360 € ▪ Antibiotics up to 5 years of age, solution oral, cost per 250 mg – 0.083 € ▪ Antibiotics from 6 years of age, tablets, cost per 250 mg – 0.062 € ▪ Methylphenidate, cost per mg – 0.019 € ▪ Nutritional supplement, cost per kcal – 0.012 € ▪ Immunoglobulins, cost per gram *In the base €51.54		

	▪ No screening group, children with SCID detected after symptoms - 1:50,000 incidence - 6.1 (1:60,000 incidence - 5.1) ▪ No screening group, children with SCID detected due to family Hx - 1.3 (1.1) ▪ No screening group, children with undiagnosed SCID - 0.7 (0.7) ▪ No screening group, children who died due to SCID - 4.2 (3.6) ▪ With screening group, children with SCID detected by screening - 8.1 (6.9) ▪ With screening group, children with SCID detected after symptoms - 0.1 (0.1) ▪ With screening group, children with ADA-SCID detected - 1.4 (1.2) ▪ With screening group, children with undiagnosed SCID - 0 (0) ▪ With screening group, children who died due to SCID - 0.8 (0.7) ▪ With screening group, number of non-SCID TCLs - 19.33 (19.33) ▪ With screening group, total suspected positives - 86.3 (85.1)		
van den Akker-van Marle 2021[196]**** Netherlands	▪ Incidence of SCID – 1:58,000 ▪ SCID patients early detected without neonatal screening – 20% ▪ Incidence of non-SCID – 1:14,000 (1:3,974; 1:2,493; 1:4,720) ▪ Non-SCID patients detected without neonatal screening – 100% ▪ Probability, survive until treatment when SCID is detected early – 94% ▪ Probability, survive after treatment when SCID is detected early – 92% ▪ Probability, survive until treatment when SCID is detected late – 78% ▪ Probability, survive after treatment when SCID is detected late – 80%		

	▪ Health status after transplantation, early/late detection, good – 80%/50% ▪ Health status after transplantation, early/late detection, moderate – 15%/30% ▪ Health status after transplantation, early/late detection, poor - 5%/20% ▪ Life expectancy after transplantation, dependent on health status, good – 65 yrs (discounted 40.8 yrs) ▪ Life expectancy after transplantation, dependent on health status, moderate – 40 yrs (discounted 30.3 yrs) ▪ Life expectancy after transplantation, dependent on health status, poor – 25 yrs (discounted 21.4 yrs) ▪ Quality of life, adjusted, utility, good – 0.95 ▪ Quality of life, adjusted, utility, moderate – 0.75 ▪ Quality of life, adjusted, utility, poor – 0.5 ▪ Number of children without SCID who get flow cytometry (plus visit to clinic) because of suspected SCID - 10/child with SCID without screening ▪ Retest on same sample - 0.39% at < 25 TREC/µl (0.28%; 0.62%; 0.62%) ▪ Second heel prick – 0.25% (0.016% + 0.003% repeated first heel pricks; 0.028% + 0.006% repeated first heel pricks; 0.061% + 0.006% repeated first heel pricks) ▪ Children with flow cytometry in total screened population – 0.08% (0.026% referrals; 0.041% referrals; 0.022% referrals) ▪ Sensitivity total screening program, SCID – 100% ▪ Sensitivity total screening program, non-SCID – 100% ▪ Distribution non-SCID into % transient, - 7.1% (na, na, na) ▪ Distribution non-SCID into % idiopathic - 2.9% (9.4%, 11.8%, 14.7%) ▪ Distribution non-SCID into % other non-SCID - 90.0% ▪ Distribution non-SCID into % secondary - N/A (56.3%, 56.9%, 51.3%) ▪ Distribution non-SCID into % syndrome - N/A (21.9%, 17.6%, 19.3%) ▪ Distribution non-SCID into % false positive - N/A (12.5%, 13.7%, 14.7%) ▪ Costs, screening test, TREC within NBS programme plus cost of retest (duplo) - €4.71 (€4.36 + devices €0.35) plus €9.42 (€6.36 per sample incl. retest; €6.36 per sample incl. retest; €6.36 per sample incl. retest ▪ Costs of second heel prick - €29.01 (blood collection €20.30 + postage €1.6 + processing €2.4 + TREC test); €79.03 ▪ Costs, diagnostics for referred children - € 1,598 (paediatrician €102), flow cytometry (€498 including clinic visit), repeat flow cytometry for 2/3 of screen positives, genetic tests of €2,000 for 1/3 (all: €7,517 SCID, €1547 secondary T-cell impairment, €8,561 idiopathic lymphocytopenia, €6,473 T-cell impairment syndromes, €985 false-positive) ▪ Costs, diagnostics in situation without screening for children with SCID or non-SCID - € 2,600 per child with SCID or non-SCID (paediatrician €102), flow cytometry (€498 including clinic visit), genetic tests (€2,000) (all: €7517 SCID, €486 secondary T-cell impairment, €2,250 idiopathic lymphocytopenia, €5,111 T-cell impairment syndromes) ▪ Costs, transplantation SCID when detected early - €90,000 ▪ Costs, transplantation SCID when detected late - €205,000

	▪ Costs, treatment non-SCID, transient - €2,200 ▪ Costs, treatment non-SCID, idiopathic - €6,200 ▪ Costs, treatment non-SCID, other - €6,200 ▪ Costs, treatment for child with SCID which dies before transplantation - €135,000 (75,000-€225,000) ▪ Costs, treatment in remaining lifetime, dependent on health status (per year), good - €26 ▪ Costs, treatment in remaining lifetime, dependent on health status (per year), moderate - €18,148 ▪ Costs, treatment in remaining lifetime, dependent on health status (per year), poor - €9,713 ▪ Costs, end of life (per year, during last 5 years), good - €0 ▪ Costs, end of life (per year, during last 5 years), moderate or poor - €6,314 because of lung disease/malign

Key: ADA - adenosine deaminase deficiency, BMT – bone marrow transplant, HSCT – hematopoietic stem-cell transplantation, IVIG – intravenous immune globulin FN – false negative, FP – false positive, QALY – quality-adjusted life year, NBS – newborn screening, NPV – net present value, PTS – post-treatment support, SESCS - Servicio de Evaluación del Servicio Canario de la Salud, SCID – severe combined immunodeficiency disease, TCL – T-cell lymphoma, TN – true negative, TP – true positive, VSL – value of statistical life, yrs – years

*The economic assessment included various conditions, explored in combination or alone. Only SCID specific values are listed here.

** Mean (95% CIs).

*** Distribution and values used in probabilistic sensitivity analysis.

**** van der Ploeg 2019 model was updated with SONNET-study data. Adaptations by screening strategy with 1) TREC ≤ 6 Copies/ 3.2 mm Punch, 2) TREC ≤ 10 Copies/ 3.2 mm Punch, and 3) new screening algorithm of direct referral if TREC levels ≤ 2 copies/3.2 punch, and cases with TREC-levels > 2 to ≤10 require a second heel prick after seven days, respectively.

Appendix 6.2 Key results from studies as presented in original currency (not adjusted to 2021 Irish Euro)

Study	ICER	Key WTP/ Benefit : Cost Ratio Outcomes
McGhee 2005[193] United States	▪ Approximately $53,560/QALY	▪ At WTP of $100,000/QALY - 86% likelihood that SCID screening would be cost-effective
Chan 2011[188] United States	▪ $25,429/LY ▪ $27,907/QALY (discounted)	▪ Screening dominant and cost-saving in all scenarios where WTP is less than $50,000/QALY *Sensitivity analysis:* ▪ A WTP of $63,000 was the point of indifference where the likelihoods of preferring screening and non-screening were equal ▪ At WTP of $50,000/QALY - screening was preferred if the SCID incidence is at least 1:250,000 ▪ If WTP were $100,000/QALY, NBS for SCID would have a 78% likelihood of being preferred
New Zealand Screening Unit 2014[194] New Zealand	▪ $30,409/LY	▪ To meet a WTP of $15,000/LY, the incidence would need to be less than the United States pilot average (1:55,100 births); or if the incidence remained at 1:104 000, the cost of the test would need to drop to $2.64 (all other parameters remaining the same)
The Institute of Health Economics 2016[192] Alberta (Canada)	▪ $332,360.39/LY	NR
Ding 2016[190] Washington (United States)	▪ $35,311/ LY	▪ Benefit to cost ratio: 5.31 at VSL of $9 million, and 2.71 at VSL of $4.2 million *Sensitivity analysis:* ▪ Varying testing cost per specimen: ICER remained <$100,000 per LY saved when all variables differed within predefined ranges ▪ Increasing the TREC cut-off reduces probability that screening is cost-effective from 65% to 58% at £20,000 per QALY and from 99% to 98%, at £30,000 per QALY

		▪ For mortality rates for the ICER to go above £20,000 or £30,000 per QALY, the pre-transplant mortality rate in the early diagnosed cohort would need to increase to 10% or 28%, respectively. For the transplant mortality rate, the mortality rate would need to increase to 17% and 36%, respectively, in the early diagnosed cohort
The National Board of Health and Welfare 2019[198] Sweden	▪	NR
Bessey 2019[101] United Kingdom	▪ £18,222 (£12,013 to £27,763)/QALY	▪ Probability screening is cost-effective at WTP of £20,0000/QALY is 65% and 99% at £30,000/QALY
van der Ploeg 2019[197] Netherlands	▪ €33,400/QALY	NR
Palko 2020[191] Finland	▪ € 14,826/ LY ▪ €15,377 /QALY*	NR for base case (see sensitivity analysis)
SESCS 2020[195] Spain	▪ Range from €18,787/QALY, if the unit cost of the screening test is €4 and the incidence is 1:50,000, to €29,640/QALY if the unit cost of the screening test is €6 and the incidence is 1:60,000.	▪ Three scenarios where ICER is higher than the WTP of €25,000/QALY: 1) if the unit cost of the screening test is €6 and the incidence it is 1:60,000; 2) when the incidence of SCID is 1:50,000 and the unit cost of the screening test is €6; and 3) when the incidence of SCID is 1:60,000 and the unit cost of the screening test is €5. *Deterministic sensitivity analysis:* ▪ Discount rate notably affects the results. If costs and benefits are not discounted, the ICER is less than €15,000/QALY ▪ If incidence of SCID was 1:50,000, key parameters which bring the ICER above the threshold of €25,000/QALY: 1) proportion of patients with a family history was greater than 30%; or 2) when an extreme odds ratio of mortality after HSCT is assumed in population with early diagnosis ▪ If incidence of SCID was 1:60,000, key parameters which bring the ICER above the threshold of €25,000/QALY: 1) proportion of patients with a family history was greater than 30%; and 2) when an extreme odds ratio of mortality after HSCT is assumed in population with early diagnosis; 3) the percentage of presumptive positives is 0.04%, 4) when the mortality before HSCT in the case of late diagnosis is 0.1786, 5) a higher number of days in non-critical care when the diagnosis is early; 6) a higher salary cost of a laboratory technician, or 7) a higher cost of HSCT

		Probabilistic sensitivity analysis ▪ Most of the points are above the cost-effectiveness thresholds of €20,000 and €25,000/QALY ▪ Probability that screening is cost-effective for a maximum threshold of €25,000/QALY is around 40%; if the WTP was €100,000/QALY, the probability that screening is cost-effective would be around 90% *Probabilistic scenario analysis* ▪ Probability that screening is cost-effective for a threshold of €25,000/QALY decreases from 43% to 34% when the test price increases from €5 to €6 there is a smaller difference when the test cost changes from €5 to €4
van den Akker-van Marle[196] 2021	▪ €41,300/QALY for the screening strategy with TREC ≤ 6 copies/3.2 mm punch; €44,100/QALY with TREC ≤ 10 copies/3.2 mm punch; €41,600/QALY for the new screening strategy**	NR (however noted that WTP between €20,000 and €80,000/QALY generally accepted in the Netherlands)

Key: HSCT – hematopoietic stem-cell transplantation, ICER – incremental cost-effectiveness ratio, INMB - incremental net monetary benefit, LY – life-years, NBS – newborn screening, NR – not reported, QALY – quality-adjusted life-year, SESCS - Servicio de Evaluación del Servicio Canario de la Salud, SCID – severe combined immunodeficiency disease, TREC - T cell receptor excision circle assay, VSL – value of statistical life, WTP – willingness to pay.
* Direct referral if TREC levels ≤ 2 copies/3.2 punch, and cases with TREC-levels > 2 to ≤10 require a second heel prick after seven days
** When similar QoL values as in the study van der Ploeg was used in sensitivity analyses.

Appendix 6.3 Estimated threshold values of variables given different WTP Thresholds

Study	Variable	WTP				
QALYs:		$25,000/QALY	$50,000/QALY	$75,000/QALY	$100,000/QALY	$150,000/QALY
McGhee 2005[193]	False negative rate	-	0.9%	45.0%	61.2%	-
	False positive rate	-	0.4%	2.1%	3.2%	-
	Test cost	-	$4.96	$9.80	$14.85	-
	Incidence	-	1:49,700	1:92,100	1:125,600	-
	Treatment cost	-	$59,900	$708,600	$1,357,300	-
	Follow-up cost	-	$280	$1,675	$3,087	-
Chan 2011[188]	Incidence	0.0000149	0.0000086	-	0.0000051	0.0000039
	Cost of screening test	$3.62	$8.46	-	$18.14	$27.82
	Cost of diagnostic test	$189.80	$673.81	-	$1641.80	$2609.80
	Specificity	0.992	0.973	-	0.934	0.896
	Sensitivity	0.99	0.610	-	0.329	0.228

		$5,000 per LY	$15,000 per LY	$30,000 per LY	$50,000 per LY	-
New Zealand Screening Unit 2014[194]	Incidence	1:23,250	1:55,100	1:102,900	1:166,650	-
	TREC Assay cost	$0.97	$2.64	$5.15	$8.49	-

Key: LY – life-years, N – number, QALY – quality-adjusted life-year, WTP – willingness to pay.

Appendix 6.4 Methodological quality assessments of individual economic evaluations using CHEC-list[186]

Items	Alberta STE 2016[192]	Bessey 2019[101]	Chan 2011[188]	Ding 2016[190]	McGhee 2005[193]	National screening unit (NZ) 2014 [194]	Palko (Finland) 2020[191]	SESCS (Spain) 2019[195]	Socialstyrelsen (Sweden) 2019[198]	Van den Akker 2021[196]	Van der Ploeg 2019[197]
Is the study population clearly described?	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Are competing alternatives clearly described?	Unclear	Yes	Yes	Yes	Unclear	Yes	Unclear	Yes	Yes	Yes	Yes
Is a well-defined research question posed in answerable form?	Yes	Yes	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Yes
Is the economic study design appropriate to the stated objective?	Yes	Yes	Yes	Unclear	Yes	Yes	Unclear	Yes	Yes	Unclear	Yes
Is the chosen time horizon appropriate to include relevant costs and consequences?	Yes	Yes	Yes	No	Unclear	Yes	Unclear	Yes	Yes	Yes	Yes
Is the actual perspective chosen appropriate?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Are all important and relevant costs for each alternative identified?	No	Yes	No	Yes	No	No	Yes	Yes	No	Unclear	Unclear
Are all costs measured appropriately in physical units?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Are costs valued appropriately?	Yes	Unclear	Yes	Yes	Yes	Unclear	No	Yes	Yes	Yes	Unclear
Are all important and relevant outcomes for each alternative identified?	Yes	Yes	Yes	Yes	No	Yes	Unclear	Yes	Unclear	Unclear	Unclear
Are all outcomes measured appropriately?	Yes	Yes	Yes	Yes	Unclear	Yes	Unclear	Yes	Unclear	Unclear	Unclear
Are outcomes valued appropriately?	Unclear	Yes	Yes	Yes	Unclear	Yes	Unclear	Unclear	Yes	Unclear	Unclear

Is an incremental analysis of costs and outcomes of alternatives performed?	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
Are all future costs and outcomes discounted appropriately?	Yes	Yes	Yes	Unclear	Yes	Yes	Unclear	Yes	Yes	Unclear	Yes
Are all important variables, whose values are uncertain, appropriately subjected to sensitivity analysis?	Unclear	Yes	Yes	No	No	No	No	Yes	No	Unclear	No
Do the conclusions follow from the data reported?	Unclear	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes
Does the study discuss the generalizability of the results to other settings and patient/ client groups?	No	Yes	Yes	Yes	No	No	No	Yes	No	Yes	Yes
Does the article indicate that there is no potential conflict of interest of study researcher(s) and funder(s)?	Yes	Yes	No	No	No	No	No	Yes	No	Yes	Yes
Are ethical and distributional issues discussed appropriately?	Yes	Yes	No	No	No	No	Yes	Yes	Yes	Yes	No
Outcome	Low	High	Moderate	Low	Low	Low	Low	High	Moderate	Low	Low

Appendix 6.5 Individual study assessments of applicability[257]

Items	Alberta STE 2016[192]	Bessey 2019[101]	Chan 2011[188]	Ding 2016[190]	McGhee 2005[193]	National screening unit (NZ) 2014 [194]	Palko (Finland) 2020[191]	SESCS (Spain) 2019[195]	Socialstyrelsen (Sweden) 2019[198]	Van den Akker 2021[196]	Van der Ploeg 2019[197]
1. Is the population relevant?	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2. Are any critical interventions missing?	Unclear	No	No	No	Unclear	No	No	No	No	No	No
3. Are any relevant outcomes missing?	Yes	No	No	No	Yes	No	No	No	No	No	No
4. Is the context applicable?	No	Yes	No	No	No	Yes	Unclear	Yes	Yes	Yes	Yes
5. Is external validation of the model sufficient?	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Unclear	Not reported	Not reported	Not reported
6. Is internal verification of the model sufficient?	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Yes	Not reported	Not reported	Not reported
7. Does the model have sufficient face validity?	No	Yes	No	Yes	No	No	Yes	Yes	No	Yes	Yes
8. Is the design of the model adequate?	Yes	Yes	Yes	Unclear	No	Yes	Unclear	Yes	Yes	Unclear	Yes
9. Are the data used in populating the model suitable?	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Unclear	Yes	Yes
10. Were the analyses adequate?	Yes	Yes	Yes	Yes	No	Yes	Unclear	Yes	Yes	Yes	Yes
11. Was there adequate assessment of uncertainty?	Unclear	Yes	Yes	No	No	No	No	Yes	No	Unclear	No
12. Was the reporting adequate?	No	Yes	Yes	Yes	No	Yes	No	Yes	Yes	No	Yes
13. Was interpretation fair and balanced?	Unclear	Yes	Yes	Yes	Unclear	Yes	Unclear	Yes	Yes	Yes	Yes
14. Were there any potential conflicts of interest?	No	No	Unclear	Yes	Unclear	Unclear	Unclear	No	Unclear	No	No
15. Were steps taken to address conflicts?	Non-applicable	Non-applicable	Unclear	Yes	Unclear	Unclear	Unclear	Non-applicable	Unclear	Non-applicable	Non-applicable

Appendix 7.1. Key assumptions of the BIA

Table A7.1 Key assumptions

Assumption	Rationale
Implementation	
The uptake rate will reflect the current uptake rate for NBS screening	Expert opinion.[204]
Modification of the existing NNBSL at Temple Street would be required to facilitate TREC-based screening for SCID.	Based on consultation with the NNBSP, there is insufficient space at the NNBSL to carry out TREC-based screening for SCID. Reconfiguration of the existing laboratory to include two additional rooms, one room for sample preparation and one for analysis, would be necessary. It was estimated that structural work would cost €80,000 to complete, and would require the oversight of a laboratory manager for 6 months.
Laboratory equipment would be bought rather than leased.	Public contracts whose monetary value exceeds €25,000 are subject to a formal tendering process prior to procurement.[207] In this context, it is challenging to estimate the leasing cost per tests without going out to tender. In the absence of reliable estimates of the cost per test, all equipment were costed as an upfront capital investment.
Two medical scientists would need to be recruited to carry out the TREC assay	The NNBSP estimated that two medical scientists would be required to carry out TREC-based screening.
Additional staff would not be required by the NNBSP.	Based on consultation with the NNBSP, additional staff would not be required within the Programme, provided that the current requirements submitted as per the current HSE National Service Plan are met.
To enable medical scientists to support out-of-hours on-call activity, stand-by cover for confirmatory flow cytometry screening is already in place for newborns with an abnormal screen for ADA-SCID.	The current capacity within the Immunology Laboratory at St James's Hospital is capable of processing the upper bound of the range of flow cytometry referrals identified in this assessment. The current capacity includes stand-by cover for processing of emergency out-of-hours samples. Based on the published literature (chapter 4), the plausible range of

There is sufficient capacity to conduct confirmatory testing for all other SCID subtypes following an abnormal TREC-based screening result within existing stand-by cover. Therefore, no additional stand-by cover is needed.	requirements for flow cytometry (range four to 72) estimated the purposes of this analysis are within the available capacity of the Immunology Laboratory at St James's Hospital. This assumption is dependent on the TREC cut-off, methodology and algorithm in use. A high rate of false positive results could create a burden on flow cytometry services in the short term, while testing protocols are being optimised.
Taxi services would be used to transport of samples from maternity hospitals following an abnormal TREC-based screening result to St James's Hospital, Dublin, for confirmatory flow cytometry testing.	As SCID is considered a paediatric emergency, use of courier services to transport samples is not considered appropriate due to the associated delivery delay. Therefore, use of taxi services is considered most appropriate. The cost of taxi transport using designated sample transport boxes supplied by the Laboratory was estimated based on the distance from each maternity hospital (n = 19) to St James's Hospital, with consideration to population geographic distribution.
Screening	
Implementation of screening for SCID does not require changes to current sample collection practices	Based on consultation with the NNBSP, no modifications to the existing NBS screening card would be necessary. No additional training of sample takers (that is, nurses, midwives or public health nurses) would be required as there would be no change to the current practice of taking four bloodspot samples. This assumption applies to the current assessment only. Requirements for the DBS sample collection card are dependent on the total number of conditions included in the NNBSP.
The unit cost per TREC test is approximately €5.	Prior to a formal tendering process, the unit cost per TREC test is challenging to estimate. In the base case analysis, the estimated deterministic value and confidence intervals were based on reported unit costs in studies included in the systematic review of cost-effectiveness (Chapter 6). However, studies frequently did not clearly report components of the cost (e.g. assay only, or including consumables and labour) making comparison between studies challenging. Uncertainty regarding the unit cost per test was investigated in OWSA and scenario analysis.

False positive TREC screens do not require investigation beyond flow cytometry	Based on consultation with the NNBSP, if a normal flow cytometry result is obtained from a case with an abnormal TREC-based screen (false positive), the Clinical Immunology Team at CHI Crumlin would contact the local paediatric team and inform them of the normal flow cytometry results. The local paediatric team who have been liaising with the parents will inform the parents of the normal flow cytometry results. No further testing is required.
All non-SCID TCLs identified by TREC requiring confirmatory flow cytometry would be in addition to current demand for flow cytometry services.	Currently, a proportion of newborns may present clinically at birth with non-SCID TCLs and initiate care pathways appropriate to the condition detected. However, as a conservative approach, it was assumed that all non-SCID TCLs would only be identified with screening for SCID using TREC. The impact of this assumption on the budget impact was investigated in scenario analysis
Diagnosis and treatment	
Verification of the TREC-based assay takes nine to 12 months. TREC-based screening for SCID begins the following year.	Based on consultation with the NNBSP, verification of the TREC-Based screening assay would take nine to 12 months. Therefore, it was assumed that TREC-based screening for SCID using the verified assay begins in the second year of the BIA. Undiagnosed SCID cases and non-SCID TCLs are identified from year two of the budget impact analysis onwards. Cases of SCID not identified early by current practices (that is, ADA-SCID screening or family history) will present clinically until completion of assay verification.
It was assumed that SCID screening including both ADA-SCID screening and TREC-based screening would have 100% sensitivity for all SCID subtypes (that is, no cases would present clinically).	The sensitivity of TREC-based screening for SCID has been estimated to be 100%.[50] However, the sensitivity of TREC-based screening for SCID is dependent on the epidemiology of SCID in the population studied. Cases of delayed-onset ADA-SCID may not be identified by TREC-based screening for SCID.[212] ADA-SCID can be detected by tandem mass spectrometry with 100% sensitivity. [204] Therefore, it was assumed that a SCID screening programme including both ADA-SCID screening by tandem mass spectrometry and TREC-based screening would identify all SCID cases.
Based on the results of flow cytometry, cases of suspected SCID undergo testing with a subset of the genetic panel. Non-SCID TCLs require confirmatory testing with the full genetic panel.	Genetic testing of case with SCID and non-SCID TCLs may be indicated to distinguish genetic disorders from acquired (that is, non-genetic) causes and guide clinical management. The primary strength of panel testing is that it provides a comprehensive analysis of genes that are

	known to cause a particular disease such as SCID, while minimizing the risk of unrelated incidental findings. Consistent with a UK CUA,[101] it was assumed that for cases of SCID, a subpanel including genes linked to the most common subtypes of SCID would be used. A comprehensive immunodeficiency panel would be indicated for non-SCID TCLs, where underlying genetic causes may not be captured by a more limited panel. Based on consultation with clinical experts, not all non-SCID TCLs would require genetic testing; in the base case analysis it was assumed that 50% of non-SCID TCLs would undergo genetic testing.
TREC-based screening will identify all cases diagnosed by clinical presentation (late diagnosis) in current practice	It is estimated that 37% of cases of SCID in Ireland present clinically (chapter 3, section 3.3.1). A quality-assured SCID screening programme including both ADA-SCID screening and TREC-based screening would have 100% sensitivity for all SCID subtypes, therefore, all cases diagnosed clinically (late) under current practice would be identified by TREC-based screening (early). Earlier identification of SCID cases has consistently been associated with cost-savings related to improved clinical outcomes (chapter 6).
TREC-based screening for SCID will identify cases of SCID not currently diagnosed by current practice.	Only one study was identified in the international literature reporting the change in prevalence following the introduction of TREC-based screening for SCID. The prevalence of diagnosed SCID increased following the introduction of TREC-based screening for SCID.[106] This study was not considered directly applicable to the Irish context due to differences in the local epidemiology of SCID and the current standard of care (that is, pre-screening). The prevalence of SCID in Ireland is estimated at 1 in 39,760 (Chapter 3). This represents the lower bound for the potential prevalence after the introduction of TREC-based screening for SCID (that is, the post-screening prevalence was assumed to be greater than or equal to the current prevalence). Based on the international literature, the highest estimated prevalence of SCID is 1 in 22,159.[108] In the base case analysis, the mid-point of the upper and lower bounds for the plausible range was assumed to represent the post-screening prevalence (1 in 28,458). In absolute numbers, this represents approximately 1 additional SCID case every second year.

Potential undiagnosed SCID cases are not of the ADA-SCID subtype.	In Ireland, ADA-SCID is currently identified by tandem mass spectrometry. Tandem mass spectrometry screening has 100% sensitivity for the detection of ADA-SCID.[204] Therefore, undiagnosed cases were assumed to be a non-ADA-SCID subtype. In addition, targeted screening in at-risk populations comprised usual care prior to the introduction of ADA-SCID screening, so it is unlikely that cases of ADA-SCID were missed by past or current practices.
The cost of HSCT includes any additional healthcare utilisation related to HSCT in the short-term post-surgery.	Chilcott et al reported that complications following transplant typically occur during the initial admission.[189] Therefore, it was this assumed that the cost of complications were included in the cost of HSCT.
Patients diagnosed clinically are admitted at the point of diagnosis.	Based on the available national clinical data for patients diagnosed with SCID, patients diagnosed clinically are typically admitted due to infectious complications and remain in hospital until definitive treatment (HSCT). It was assumed that the cost of diagnostic follow-up is captured in the cost of inpatient admission for these patients.
Inpatients care costs for non-SCID TCLs are reflective of the typical patient.	In the absence of evidence, it was assumed that non-SCID TCLs requiring hospital admission would incur the same inpatient care costs as the average patient admitted for disorders of the immune system.

Key: ADA-SCID - Adenosine Deaminase Deficiency Severe Combined Immunodeficiency; CHI - Children's Health Ireland, CUA – cost-utility analysis; HSCT - haematopoietic stem cell transplantation; HSE – health Service Executive; NA – not applicable; NNBSP – National Newborn Bloodspot Screening Programme; OWSA – one-way sensitivity analysis; SCID - severe combined immunodeficiency, TCL - T cell lymphopenia; TREC- T-cell receptor excision circles.

Appendix 8.1 Summary of steps required when adding a new screen to the NNBSP: ADA-SCID example.[17]

The below was included in a 2021 HIQA report and outlines a case example of the process involved in the addition of ADA-SCID to the NNBSP:

1. Define screening case definition for ADA-SCID

2. Verification of CE-marked diagnostic newborn bloodspot screening dried blood spot tandem mass spectrometry test kit. This process includes the following steps:

    a. Engage with kit supplier to schedule a technical specialist to come on site to the NNBSL and optimise kits on the existing laboratory tandem mass spectrometers

    b. NNBSL draft and approve a laboratory verification plan for ADA-SCID, to include re-verification of five existing mass spectrometry screens (PKU, MSUD, HCU, GA1 and MCADD)

    c. Verification experiments, which examine, at a minimum, precision, accuracy, analytical sensitivity, linearity, and instrument comparisons.

    d. Clinical studies, comparison with an existing method, and inter-laboratory comparisons, where possible.

3. Decide on dried blood spot sample criteria for laboratory verification process in order to establish population distribution statistics and associated 95% Confidence Intervals.

Samples must be:

- anonymized
- of good quality
- obtained from babies who are:
    - no more than two weeks old
    - greater than 36 weeks gestational age
    - not transfused
    - on normal feeds.
- taken at between 72 and 120 hours
- Data to be collected must include:
    - mean

- median
- percentiles.

4. Establishment of cut-offs, based on percentile data, for all conditions screened on the tandem mass spectrometer (MS/MS). This involves acquisition of percentile data from a large number of newborn screening samples (>5,000) using criteria defined above.

5. Engagement between NNBSL and the Laboratory Information Management System (LIMS) provider. This involves defining software changes necessary to implement all required changes to various components of the LIMS for addition of the new condition. The testing algorithm is integrated into the existing LIMS, followed by extensive testing for all result permutations.

6. Development, testing and integration of follow-up protocols into the current LIMS. Reconfiguration of electronic and hard copy patient reports to accommodate the new analyte is also required.

7. Quality assurance: it must be ensured that all laboratory procedures are in compliance with ISO 15189 (the international standard for requirements for quality and competence within medical laboratories).

8. Scoping and agreement of the protocol for follow-up of a screen positive result on routine dried bloodspot samples. This protocol should be in line with existing NNBSL procedures for other screen positive conditions.

9. Decide on second tier follow-up protocol and agree algorithm for this.

10. Scope and agree the clinical pathway for screen positive babies:

    a. Identify the clinical centres or laboratories that will be responsible for follow-up diagnostic testing and for pathways for samples into and out of these centres.

    b. Identify the clinical centres responsible for follow-up care and treatment, and the pathway for patients into the clinical centre.

11. Select suitable key performance indicators (KPIs) for the programme, for example, laboratory turnaround time for samples and time until either clinical review and reassurance or diagnosis. Monitor these KPIs as part of the programme.

12. Establish processes for monitoring of usual parameters for screening programme quality assurance. Examples of such parameters include sensitivity, specificity, positive predictive value, and negative predictive value.

13. Consider programme review and check points for quality assurance.

Communication plan

A communication plan is required for all stakeholders. Such stakeholders include, at a minimum:

- parents
- public health nurse representation (Director of Public Health Nursing)
- midwife and maternity unit representation (Director of Midwifery)
- clinical teams in maternity units and paediatric hospitals which receive referrals for screen positive patients.

In particular, clinical teams need to be aware of, and support and follow, agreed pathways for further investigation and follow-up.

The following also require revision when a new screen is added to the overall programme:

- NBS website
- parent information leaflets, including translations
- training modules such as those hosted on HSE's online learning and development portal 'HSELanD'
- 'A Practical Guide to Newborn Screening in Ireland'
- sample takers' guide
- HSE Standard Operating Procedure.

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