Health Information and Quality Authority

An tÚdarás Um Fhaisnéis agus Cáilíocht Sláinte

Protocol for the health technology assessment of the addition of severe combined immunodeficiency (SCID) to the National Newborn Bloodspot Screening Programme

Version 1.1

4 October 2022

Version history

Version	Date	Amendments made
1.0	Published 4 March 2022	Original version
1.1	Published 4 October 2022	Addition of domains for 'phase two' of the assessment, following decision by National Screening Advisory Committee (NSAC) to proceed to phase two on the basis of the findings of phase one.

About the Health Information and Quality Authority

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.

Table of Contents

List of abbreviations used in this document

ADA	adenosine deaminase
CHEERS	Consolidated Health Economic Evaluation Reporting Standard
DBS	dried blood spot
EUnetHTA	European Network for Health Technology Assessment
HIQA	Health Information and Quality Authority
HSE	Health Service Executive
HTA	health technology assessment
ICER	incremental cost-effectiveness ratio
NMB	net monetary benefit
NNBSP	National Newborn Bloodspot Screening Programme
NSAC	National Screening Advisory Committee
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PICOS	Population, intervention, comparator, outcomes, study design
RT-qPCR	real time-quantitative polymerase chain reaction
SCID	severe combined immunodeficiency
TCL	T cell lymphopenia
TREC	T cell receptor excision circles

Background to the HIQA/NSAC work programme

In 2018, the Scoping Inquiry into the CervicalCheck Screening Programme by Dr Gabriel Scally ('the Scally Report'), recommended establishing 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 developing and considering 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 and provides evidence-based advice to NSAC on behalf of the Minister for Health.

1. Introduction

1.1 Background

Newborn bloodspot screening commenced in Ireland in 1966 with the development of a national screening programme for phenylketonuria (PKU). Currently, in Ireland, the National Newborn Bloodspot Screening Programme (NNBSP) screens for nine conditions:[1]

- phenylketonuria
- homocystinuria
- maple syrup urine disease
- classical galactosaemia
- congenital hypothyroidism
- cystic fibrosis
- medium chain acyl-CoA dehydrogenase deficiency
- glutaric aciduria type 1
- adenosine deaminase deficiency severe combined immunodeficiency (ADA-SCID)

Participation in the NBS programme in Ireland is high, with an estimated uptake of 99.9%. Each year, approximately 60,000 infants are born in Ireland, and the NNBSP identifies approximately 110 babies in Ireland with one of the conditions screened for through the programme.[1]

SCID is an inherited inborn error of immunity. It is one of the most severe forms of primary immunodeficiency.[2, 3] SCID is caused by mutations in at least 19 known

genes and is characterised by T cell lymphopenia (TCL). This condition (TCL) involves an absence or significantly depleted level of functioning of T-cells, with varying impacts on B-cells and Natural Killer (NK) cells, depending on the gene affected.[3, 4] ADA-SCID is one specific form of SCID, with Ireland having a comparatively high prevalence of ADA-SCID (as a proportion of all SCID cases) relative to other countries (50% of cases relative to 12% in the United States).[5] Following a recommendation from NSAC on 17 July 2020, which was subsequently approved by the Minister for Health, screening for ADA-SCID by the NNBSP formally commenced on 23 May 2022.[6, 7]

At the time of the recommendation concerning ADA-SCID, the HSE NNBSP Governance Group also requested potential consideration of screening for the remaining subtypes of SCID. Specifically, the NNBSP Governance Group proposed screening all newborns for SCID via the method of quantification of T-cell receptor excision circles (TREC). In September 2021, at the request of NSAC, HIQA agreed to undertake a HTA of the addition of severe combined immunodeficiency (SCID) to the NNBSP. The present document describes the evidence synthesis approach that will be adopted in the HTA.

1.2 Condition and screening technology

T cells (or T lymphocytes) are major components of the adaptive immune system, which help to fight infection. SCID is typically asymptomatic at birth but leads to severe and recurrent infections in the first year of life.[8] Due to their immunodeficiency, children with SCID are also vulnerable to infections associated with the injection of live vaccines.[9] Without treatment, SCID is uniformly fatal and therefore it is recognised as a paediatric emergency.

SCID can be detected by quantifying T cell receptor excision circles (TRECs) in dried blood spots (DBS).[10] TRECs are a DNA by-product generated within the thymus during gene rearrangement of T cell receptors. TREC levels in the peripheral blood are a biomarker of recent thymic function and can be used to detect impaired T cell development, with low levels indicative of TCL.[11] Therefore, TREC levels can be used to detect impaired T cell development and screen for SCID. TREC quantification is performed using real-time quantitative polymerase chain reaction (RT-qPCR) assays.

1.3 Evidence synthesis 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. HTAs are

designed to inform safe and effective health policies that are both patient-focused and achieve the best value.

The HTAs conducted by HIQA's HTA Directorate follow the HTA Core Model® proposed by the European Network for Health Technology Assessment (EUnetHTA).[12] As per the Core Model, HTAs conducted by HIQA's HTA Directorate commonly include the following domains:

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

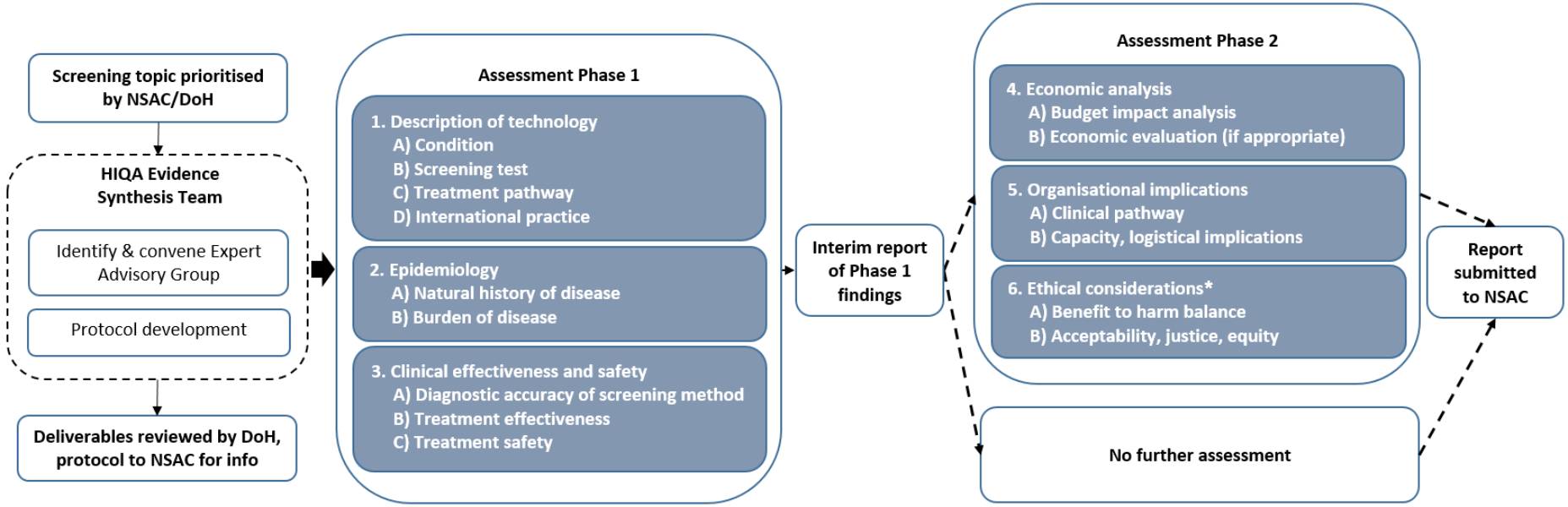
Given the resource-intensive nature of HTA and the need for responsive evidence-based decision-making, the evidence synthesis approach adopted for assessing population-based screening programmes (that is, to support NSAC advice to the Department of Health) will follow a stepwise (two-phase) process. An overview of this process is presented in Figure 1.

In the first phase, evidence synthesis underpinning TREC-based screening for SCID will be conducted for the domains of the description of the technology, epidemiology, and clinical effectiveness (including assessment of safety). Subject to the findings of these HTA domains, a second phase may be undertaken to assess the economic, organisational, social, ethical and legal implications of introducing TREC-based screening for SCID in Ireland.

HIQA will convene a multidisciplinary expert advisory group (EAG) to advise the Evaluation Team during the course of the HTA. The role of the HIQA EAG is to inform and guide the process, provide expert advice and information, and to provide access to data where appropriate.

On the basis of the findings of phase one of this assessment, in May 2022, NSAC requested HIQA to proceed to phase two.

Figure 1. HTA process flow to inform NSAC advice on NNBSP



Key: DoH – Department of Health; HTA – health technology assessment; NNBSP – National Newborn Bloodspot Screening Programme; NSAC – National Screening Advisory Committee.

*May further include social and legal considerations, as appropriate.

1.4 Aims and objectives

In the subsequent sections of this protocol, the scope and methods of the HTA are described according to the HTA domains that will be assessed in the first phase (that is, description of the technology, epidemiology, clinical effectiveness and safety). The objectives of this HTA are as follows:

Phase one

- 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 and safety of early treatment compared with late treatment for SCID.

Phase two

- evaluate the cost effectiveness of newborn screening for SCID
- estimate the resource and budget implications of introducing newborn screening for SCID in Ireland
- consider any wider organisational, ethical or societal implications that newborn screening for SCID may have for children, families, the general public or the healthcare system in Ireland.

The NSAC has established a list of 20 criteria for appraising the viability, effectiveness and appropriateness of a national population-based screening programme.[6] These 20 criteria are grouped under five categories, as follows:

- the condition
- the screening method
- the intervention
- the screening programme
- implementation.

The HIQA HTA team performed a mapping exercise to identify how the typical domains of a HTA, as per the HTA Core Model® [12], relate to the NSAC criteria. This mapping exercise aimed to clarify the extent to which the output of a HTA might

address the NSAC criteria, and which section of the HTA addresses which criterion/criteria. A full list of the NSAC criteria and their corresponding HTA domains, as identified by HIQA, is presented in Appendix 1.

2. Description of technology

The purpose of the description of technology chapter within the HTA is to provide an overview of the population-based screening programme being assessed. The specific aims of this chapter will be to describe:

- the current diagnostic and treatment pathway for children with SCID (including follow-up) in Ireland
- the method of TREC-based screening for SCID in newborns (including diagnostic follow-up to a positive screen to establish a specific genetic diagnosis)
- international practice in the use of TREC-based screening for SCID in newborns.

Further details on these aims are described in sections 2.1 to 2.3.

2.1 Current diagnostic and treatment pathway

This section will comprise an overview of the diagnostic and treatment pathway. It will be informed by a review of international clinical guidelines (including the European guidelines for the treatment of children with immunodeficiencies), publicly available literature, consideration of current Irish pathways, and by expert clinical opinion. Haematopoietic stem cell transplantation (HSCT) is currently the primary treatment option for children diagnosed with SCID.[13]

2.2 TREC-based screening for SCID in newborns

The method of TREC-based screening for SCID in newborns (that is, the technology) will be described in detail. This description will be informed by review of publicly available literature and expert opinion, as appropriate. Of note, the focus of this assessment is to inform a decision in relation to population-based screening for SCID as part of the NNBSP and, as such, the use of targeted genomic screening is outside the scope of the assessment. Where applicable, the use of gene testing methods will be noted with respect to their use as part of the existing diagnostic pathway.

2.3 International practice

An overview of international practice, describing the countries that currently have newborn bloodspot screening programmes in place for SCID and the screening tests used, will be provided. The overview will be informed by reviewing grey literature sources (for example, national public health organisations, and the websites of governmental departments and relevant agencies), and recent peer-reviewed literature.[14-17] The overview will focus on countries of most relevance to Ireland, including:

- countries in the European Economic Area
- the UK
- the US
- Canada
- Australia
- New Zealand.

3. Epidemiology

SCID covers a broad spectrum of genetic diseases characterised by a pronounced cellular and humoral immune deficiency (that is, defects in both T and B cell responses).[9] The subtypes of SCID can be classified according to the immune cells (T cells, B cells and or natural killer (NK) cells) that are defective or by the molecular basis of disease. The known subtypes will be presented according to their description within the clinical literature and the Irish context where possible. The gathered literature and clinical data on the genetic patterns of inheritance, symptom presentation and natural history of SCID and subtypes of SCID will also be presented.

Where available, national data (such as from the database in the Department of Paediatric Infectious Diseases and Immunology, Children's Health Ireland at Crumlin, Dublin) and relevant international data on the morbidity and mortality associated with SCID will be presented. The specific aims of this chapter will be to describe:

- SCID and its subtypes
- the aetiology/pathology, symptoms and natural progression of SCID and its subtypes
- the burden (morbidity and mortality) of SCID.

4. Clinical effectiveness of screening

Evidence underpinning the screening method and treatment is central to decision-making regarding the expansion of newborn bloodspot screening. Accordingly, this HTA chapter aims to establish the:

- test accuracy of TREC-based screening for SCID, including consideration of potential harms (such as the impact of false positives) and incidental findings
- clinical benefits of early compared with late treatment and, specifically, early versus late HSCT.

Systematic reviews will be undertaken to identify, appraise and synthesise relevant international literature that addresses these topics. The proposed review questions and methods are outlined below.

4.1 Test accuracy

4.1.1 Overview

The aim of this systematic review is to assess the test accuracy of TREC-based screening for SCID. The review's methods have been informed by previous systematic reviews undertaken in this area.[10, 18]

From a methodological perspective, studies assessing test accuracy are known as diagnostic test accuracy (DTA) studies, where the intended use of the test can be for diagnosis, screening, staging, monitoring, surveillance, prognosis, treatment selection or other purposes.[19] Within this HTA, the term "test accuracy" will be used in lieu of DTA to minimise potential confusion in terms of the diverging purposes of screening and diagnostic tests.

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). Given the nature of the screening programme under consideration, 'test accuracy' will in this case, reflect the proportion of those with a positive test using TREC analysis that subsequently have a positive confirmatory diagnosis. If the initial TREC test is normal, no further testing is performed as part of the screening programme and so it is not possible to calculate a false negative rate for the programme. Estimates of positive predictive value and false positivity may be provided, in line with previous

reviews in this area.[10] Where a study reports instances of missed cases, this will be documented.

4.1.2 Review question

The review question was formulated according to the Population, Index test, Reference test, Diagnosis (PIRD) framework (presented in Table 1).[20] The systematic review seeks to answer the following question:

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

Table 3. Review question for assessing test accuracy of TREC assay

Population	Newborns
Index test	TREC assay using DBS
Reference standard	Flow cytometry, T-cell proliferation assays, genetic testing, and or subsequent clinical diagnosis of SCID
Diagnosis of interest	SCID*
Eligibility criteria	**Include:** ▪ Cross-sectional, case-control and cohort studies. **Exclude:** ▪ Non-human studies, studies that include less than five newborns, papers not available in English, letters, editorials, commentaries, preprints and conference abstracts, pre-prints, studies published before 2010.**

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

* Although the TREC assay identifies infants with severe T cell lymphopenia at birth, it does not provide a SCID diagnosis; confirmatory tests are required to provide a definitive diagnosis.[21]

** Scoping for this review indicated that over 90% of studies examined in previous reviews were published from 2010 onwards.

4.1.3 Eligible study design

Cross-sectional, case-control, cohort and case series studies will be eligible for inclusion. Where a sufficient quantity of studies with clinical study designs (for example, cohort studies with population-based participation) are included, studies that are ranked lower in the hierarchy of evidence (for example, analytical studies in which both clinical samples and controls are assessed in combination or where the study's aim is to establish an optimal cut-off only) will be excluded.

4.1.4 Search methods

Electronic searches will be conducted in Medline (EBSCO), Embase (OVID) and the Cochrane Library, supplemented by a grey literature search of national and international electronic sources. Forward citation searching and searching of the reference lists of included studies will also be undertaken. The full search strategy is presented in Appendix 2.

4.1.5 Data collection and analysis

Selection of studies

All citations (titles and abstracts), as well as full texts of potentially eligible studies, will be screened independently by two reviewers as per the inclusion criteria, with disagreements resolved by discussion. Screening will be undertaken using Covidence software.

Data extraction and management

Data extraction will be performed by one reviewer using Microsoft Excel software. All data extracted will be reviewed by a second person, with disagreements resolved by discussion. A standardised data extraction template will be developed prior to undertaking the systematic review. Relevant data include:

- population characteristics (country, sample size)
- comparator (for example, follow-up diagnostic testing)
- general accuracy measures
- TREC cut-off value(s)
- number of re-tests on initial DBS samples (defined as testing additional punches from the initial Guthrie card)
- number of repeat (requiring collection of a second sample) DBS samples requested
- diagnoses detected (including incidental findings) or not detected
- incidence of SCID and TCL.

Risk of bias assessment

Where studies present the results of the index test and reference standard for all participants screened, methodological quality will be assessed using the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool.[22] As there is no existing tool available to appraise the quality of studies that report test accuracy without a reference standard, a narrative summary will be provided of the reporting and completeness of such studies. Each study will be assessed by one reviewer, with the assessment cross-checked by a second reviewer.

Data synthesis

If data of sufficient quantity, quality and homogeneity are identified, meta-analysis will be considered and undertaken if appropriate. If this is not the case, the findings of the included studies will be narratively synthesised. The synthesis will include a discussion on the potential harms from the use of TREC-based screening (for example, the potential for false positives).

4.2 Treatment effectiveness

4.2.1 Overview

Haematopoietic stem cell transplantation (HSCT) is currently the main treatment option for children diagnosed with SCID.[13] However, other treatments, including gene therapy and enzyme replacement therapy, are also considered options for treatment of individuals with ADA-SCID. This review aims to assess the clinical benefits associated with providing earlier HSCT treatment to infants with SCID (that is, before the onset of symptoms). The methods of the systematic review have been informed by published literature and expert opinion.[18, 23-25]

Haematopoietic stem cell transplantation (HSCT)

This systematic review aims to assess the clinical benefits of early HSCT following newborn screening for SCID compared with late HSCT following symptomatic presentation. Allogeneic HSCT from a healthy human leukocyte antigen-matched sibling or family donor is considered the gold standard therapeutic option for infants diagnosed with SCID.[13] Evidence to date demonstrates that HSCT is an effective treatment for SCID patients, but effectiveness is influenced by a number of factors such as availability of matched-related donors, history of infection and whether early transplantation is undertaken.[18] HSCT outcomes can also be impacted by the use of a conditioning regimen, and the regimen chosen.[13] As the current standard of care for patients with SCID,[26] the safety of HSCT will only be considered from the perspective of potential additional adverse events associated with earlier versus late transplant.

Other therapies for treating SCID

There is currently only one gene therapy licensed by the European Medicines Agency for use in the European Union.[27, 28] The gene therapy, which has orphan designation from the European Commission,[29] is indicated for treatment of individuals with ADA-SCID that do not have a suitable, matched donor. Irish patients can be referred with E112 approved funding under the Treatment Abroad Scheme.[30] Given the intended inclusion of ADA-SCID in the list of conditions screened for in the existing NNBSP (this inclusion being under implementation as of November 2021)[6] it is expected that the treatment pathway of individuals with

ADA-SCID would not be impacted by the introduction of TREC-based screening for SCID. Given that HSCT remains the therapy of choice for treatment of SCID and that licensed gene therapy is currently only available for treatment of individuals with ADA-SCID, the safety and effectiveness of gene therapy will not be evaluated in this review. However, an overview of the current status of gene therapy for SCID and the most recent high-quality literature will be presented in the HTA.

Enzyme replacement therapy is available as a bridging therapy for infants with ADA-SCID that are awaiting HSCT or gene therapy.[13] However, there is no benefit associated with the use of enzyme replacement therapy for infants with non-ADA forms of SCID. Therefore, the clinical effectiveness and safety of enzyme replacement therapy will not be assessed as part of this review.

4.2.2 Review question

The review question was formulated according to the Population, Intervention, Comparator, Outcomes and Study design (PICOS) framework. The review seeks to answer the following question:

- What is the clinical effectiveness and safety of early HSCT (that is, diagnosis prior to the onset of symptoms and use of pre-transplant supportive care to prevent infection) compared with late HSCT (that is, clinical diagnosis following presentation of symptoms) in those diagnosed with SCID?

Table 4. Review question for assessing the benefits of early treatment

Population	Infants or children with SCID
Intervention	Early HSCT following diagnosis at birth (for example, through universal newborn screening, familial or incidental detection).
Comparator	Late HSCT (defined as following symptomatic presentation) or no treatment.
Outcomes	▪ survival ▪ freedom from immunoglobulin substitution ▪ CD3+ T-cell and IgA recovery ▪ any other cognitive, behavioural and neurological outcomes ▪ safety (for example, incidence of adverse events associated with early HSCT).
Study design	Retrospective or prospective cohort studies or analyses.
Eligibility criteria	**Exclude:** ▪ Non-human studies, case studies, papers not available in English, letters, editorials, commentaries, preprints, conference abstracts and studies published pre-2000.*

Key: HSCT – haematopoietic stem cell transplant; SCID – severe combined immunodeficiency.
* Scoping for this review indicated that over 90% of studies examined in previous reviews were published from 2000 onwards.

4.2.3 Eligible study design

Retrospective and prospective cohort studies, in which the clinical outcomes of SCID patients with an early diagnosis and compared with those that received a late diagnosis, will be eligible for inclusion.

4.2.4 Search methods

Electronic searches will be conducted in Medline (EBSCO), Embase (OVID) and the Cochrane Library, supplemented by a grey literature search of national and international electronic sources. Forward citation searching and searching of the reference lists of included studies will also be undertaken. The full search strategy is presented in Appendix 2.

4.2.5 Data collection and analysis

Selection of studies

All citations (titles and abstracts) as well as full texts of potentially eligible studies will be screened independently by two reviewers as per the inclusion criteria, with disagreements resolved by discussion. Screening will be undertaken using Covidence software.

Data extraction and management

Data extraction will be performed by one reviewer using Microsoft Excel software. All data extracted will be reviewed by a second person, with disagreements resolved by discussion. A standardised data extraction template will be developed prior to undertaking the review. Relevant data include:

- country
- study design
- source of study data
- sample size (by exposed, non-exposed group)
- population characteristics (age at diagnosis/transplant, gender, SCID subtype)
- diagnostic method
- donor type
- illness/infection prior to HSCT
- treatment prior to HSCT
- definition of early/late HSCT
- incidence of repeat HSCT
- conditioning regimens used
- length of follow-up
- findings at follow-up
- survival outcomes (before/after transplant, statistical findings in relation to age at transplantation).

Risk of bias assessment

Each study will be assessed by one reviewer, with the assessment cross-checked by a second reviewer. The National Heart, Lung and Blood Institute (NIH) quality assessment tools will be used for appraisal of observational cohort studies. The Joanna Briggs Institute critical appraisal tools will be used for cross-sectional and case control studies. Study quality will be rated as good, fair or poor.

Data synthesis

If data of sufficient quantity, quality and homogeneity are identified, meta-analysis will be considered and undertaken if appropriate. If this is not the case, the findings of the included studies will be narratively synthesised.

5. Cost effectiveness

5.1 Systematic review of cost-effectiveness studies

A systematic review of the literature on the cost effectiveness of TREC-based newborn screening for SCID will be conducted. The findings of this review may

adequately inform the question regarding the cost effectiveness of screening for SCID or may indicate the need for a de novo economic model for the purposes of evaluating the cost effectiveness of newborn screening for SCID in Ireland. The reporting of this systematic review will adhere to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria.[31] This review will also follow national guidelines for the retrieval and interpretation of economic literature.[32]

5.1.1 Research question

The research question for this systematic review is:

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

The associated Population, Intervention, Comparator, Outcomes, and Study design (PICOS) framework is provided in Table 5.

Table 5. PICOS framework for systematic review of cost-effectiveness studies

Population	Children
Intervention	TREC-based newborn screening for all SCID
Comparator	▪ no newborn screening for SCID (with identification based on risk-based detection at birth or clinical presentation) ▪ 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: ICER – incremental cost-effectiveness ratio; NMB – net monetary benefit; TREC – T-cell receptor excision circles; SCID – severe combined immunodeficiency

5.1.2 Search methods for identification of studies

Electronic searches will be conducted in Medline, Embase and the Cochrane Library (which includes the Database of Systematic Reviews, the Database of Abstracts of Reviews of Effects (DARE), the Health Technology Assessment Database (HTA) and the National Health Service Economic Evaluation Database (NHS EED)). Electronic database searches will be supplemented by a search of grey literature including Google Scholar, national and HTA electronic sources. Reference lists of included studies will be searched for potentially relevant citations.

The search string was developed in consultation with a HIQA librarian and is presented in Appendix 2.

Study designs

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 consequences of two or more alternative strategies are compared).[33, 34] During scoping work completed to inform this protocol, it was noted that the majority of the economic analyses returned were in the form of cost-effectiveness analyses, cost-utility analyses 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 will be considered (that is, cost-utility analyses or cost-effectiveness analyses). Where other forms of cost analyses are identified, these will not be retained for inclusion in the review of cost-effectiveness studies, but will be retained for later consideration in informing the budget impact analysis.

Exclusion criteria

The following exclusion criteria will be 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 is not available

5.1.3 Data collection and analysis

Selection of studies

Titles and abstracts will be screened independently by two reviewers. The full text of potentially eligible studies will be retrieved and independently assessed for eligibility by two reviewers according to the criteria outlined in Table 5, with any disagreements being resolved by discussion or a third reviewer, if required.

Data extraction and management

A data extraction form will be developed and piloted. Data will be extracted by one reviewer and cross-checked in full by a second with any disagreements resolved through discussion or a third reviewer where necessary.

Assessment of methodological quality and transferability

Assessment of the methodological quality of economic evaluations will be carried out using the Consensus on Health Economics Criteria (CHEC)-list.[35] The ISPOR questionnaire will be used to assess the transferability potential of economic evaluations to the Irish setting.[36] This will be performed by two people independently with any disagreement resolved through discussion or a third reviewer where necessary.

Data synthesis

Given the likely heterogeneity of studies in terms of population and healthcare system characteristics, and in line with previous assessments on this topic conducted internationally,[37, 38] results will be synthesised narratively. To facilitate comparability of the results across countries and years, where appropriate, costs will be converted to euro in accordance with national HTA guidelines.[32]

5.1.4 De novo economic evaluation

Contingent on the findings of the systematic review of cost-effectiveness studies described above, a de novo economic evaluation may be considered appropriate. This will be judged based on elements such as the applicability of international evidence to the Irish context, the availability of Irish data that may strengthen existing estimates, and the overall value of performing such analysis in terms of informing decision-making. If a de novo economic evaluation is considered necessary, this will be conducted to estimate the cost effectiveness of screening for SCID compared with usual care (that is, ADA-SCID screening and targeted surveillance of those with a positive family history) in accordance with national HTA guidelines and Consolidated Health Economic Evaluation Reporting Standards (CHEERS) reporting guidelines.[12, 39]

5.2 Budget impact analysis and organisational implications

A budget impact analysis (BIA) will be undertaken to inform whether expansion of the NNBSP to include screening for SCID is likely to be affordable. The analysis will estimate the costs to the HSE associated with implementing this form of screening over an initial five-year time horizon, reported in terms of incremental annual cost. The comparator will be the current standard of care in Ireland. As of 23 May 2022, this is population based screening for ADA-SCID with the remaining SCID subtypes detected through family history or clinical presentation.

Parameter data will be obtained from Irish data sources and published literature as appropriate (including the consideration of cost analyses identified during the systematic review of cost-effectiveness studies). Input from the HIQA EAG will be required to inform plausible values. In addition to the cost of tests and laboratory equipment, changes to organisational processes (for example, clinical pathways) resulting from the addition of SCID to the NNBSP will be identified and considered as part of the BIA. Furthermore, potential cost offsets, such as prevention of hospitalisation, will also be considered and included, if appropriate.

The analysis will be carried out from the perspective of the publicly funded health and social care system in Ireland. Sensitivity analyses will be conducted to assess uncertainty within the BIA.

Key parameter data required for the analysis may include:

- estimates of the target population and likely uptake rates
- estimates of the number of cases of SCID, non-SCID TCL, and instances of false positives likely to be identified by this form of screening programme

- estimates of the incremental costs associated with diagnosis and treatment of SCID cases identified
- capital investment for laboratory equipment (alongside necessary maintenance), laboratory space and storage, and any additional requirements to accommodate testing
- laboratory and clinical implementation costs (for example, consumables, verification, establishment of cut-off values, development of screening algorithms and pathways, information and communications technology (ICT) upgrades)
- training and education of laboratory staff (as this form of screening would be a new technology in the NNBSL)
- training and education for clinical staff involved in the delivery of the NNBSP
- any additional recruitment requirements to facilitate implementation and ongoing performance (for example, performance of TREC-based tests and routine quality assurance associated with same) of this form of screening (for example, laboratory and clinical staff)
- costs for confirmatory testing and clinical evaluation
- costs for updating NNBSP material and an information campaign
- any potential broader organisational issues associated with the sequential addition of conditions to the NNBSP.

The assessment of necessary organisational changes will be carried out in accordance with the EUnetHTA Core Model.[12] A description of the current pathway for the NNBSP, any anticipated changes in the organisation of care as a result of the introduction of screening for SCID and the impact on existing activities will be provided. The impact of screening for SCID on various types of resources (such as, equipment and supplies, facilities, and human resources) will be considered as outlined above.

6. Ethical and social considerations

The ethical analysis will consider key social and moral norms and values relevant to newborn screening for SCID. Key ethical issues outlined in the EUnetHTA Core Model will be used to guide the ethical analysis.[12] Potential ethical issues may include issues related to:

- informed consent in the context of the likelihood of conditions other than SCID being identified by such a screening programme
- potential benefits for those with SCID associated with earlier diagnosis and hence earlier access to treatment, likely improved outcomes, avoidance of harms relating to live vaccines and a potential reduction in the 'diagnostic odyssey' (that is, 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 potential for uncertainty in the clinical meaningfulness, clinical course, and or treatment availability for those identified as having non-SCID TCLs, alongside the possibility of increasing the diagnostic odyssey for these patients identified in the course of screening for SCID
- instances of false positives, the associated burden of confirmatory testing, and the related potential for emotional distress and anxiety
- communication of screening and confirmatory testing results
- any broader implications of screening for the family of the newborn.

7. Anticipated timeline

It is expected that a draft report of this HTA will be completed by October 2022. However, this timeline is dependent on available resources and the extent of the literature. The draft report will then be circulated and reviewed at a meeting of the HIQA EAG. Necessary amendments and revisions to the draft report will be made following the meeting of the HIQA EAG before the final report is circulated to NSAC for consideration (expected delivery early December 2022).

References

1. Health Service Executive. A Practical Guide to Newborn Bloodspot Screening In Ireland: 8th edition 2021 [Available from: https://www.hse.ie/eng/health/child/newbornscreening/newbornbloodspotscreening/information-for-professionals/a-practical-guide-to-newborn-bloodspot-screening-in-ireland.pdf.
2. Kwan A, Puck JM, editors. History and current status of newborn screening for severe combined immunodeficiency. Seminars in perinatology; 2015: Elsevier.
3. Tangye SG, Al-Herz W, Bousfiha A, Chatila T, Cunningham-Rundles C, Etzioni A, et al. Human inborn errors of immunity: 2019 update on the classification from the International Union of Immunological Societies Expert Committee. Journal of clinical immunology. 2020;40:24-64.
4. European Society for Immunodeficiencies. Working definitions for clinical diagnosis of PID 2019 [Available from: https://esid.org/Working-Parties/Registry-Working-Party/Diagnosis-criteria.
5. Burns H, Collins A, Marsden P, Flood TJ, Slatter MA, Booth C, et al. Severe Combined Immunodeficiency (SCID)-the Irish Experience. Journal of clinical immunology. 2021.
6. Department of Health. National Screening Advisory Committee: Recommendations 2021 [Available from: https://www.gov.ie/en/publication/5af1dd-national-screening-advisory-committee-recommendations/.
7. Department of Health. National Screening Advisory Committee: Recommendations 2022 [Available from: https://www.gov.ie/en/publication/5af1dd-national-screening-advisory-committee-recommendations/.
8. Rivers L, Gaspar HB. Severe combined immunodeficiency: recent developments and guidance on clinical management. Archives of disease in childhood. 2015;100:667-72.
9. Audrain MAP, Léger AJC, Hémont CAF, Mirallié SM, Cheillan D, Rimbert MGM, et al. Newborn Screening for Severe Combined Immunodeficiency: Analytic and Clinical Performance of the T Cell Receptor Excision Circle Assay in France (DEPISTREC Study). Journal of clinical immunology. 2018;38:778-86.
10. van der Spek J, Groenwold RH, van der Burg M, van Montfrans JM. TREC Based Newborn Screening for Severe Combined Immunodeficiency Disease: A Systematic Review. Journal of clinical immunology. 2015;35:416-30.
11. Serana F, Chiarini M, Zanotti C, Sottini A, Bertoli D, Bosio A, et al. Use of V(D)J recombination excision circles to identify T- and B-cell defects and to monitor the treatment in primary and acquired immunodeficiencies. Journal of translational medicine. 2013;11:119.
12. European Network for Health Technology Assessment (EUnetHTA). HTA Core Model [Available from: https://www.eunethta.eu/hta-core-model/.
13. Wahlstrom JT, Dvorak CC, Cowan MJ. Hematopoietic Stem Cell Transplantation for Severe Combined Immunodeficiency. Current pediatrics reports. 2015;3:1-10.
14. Health Information and Quality Authority. Review of processes in use to inform

the expansion of newborn bloodspot screening programmes. 2021.
15. Quinn J, Orange JS, Modell V, Modell F. The case for severe combined immunodeficiency (SCID) and T cell lymphopenia newborn screening: saving lives...one at a time. Immunologic research. 2020;68:48-53.
16. Loeber JG, Platis D, Zetterström RH, Almashanu S, Boemer F, Bonham JR, et al. Neonatal Screening in Europe Revisited: An ISNS Perspective on the Current State and Developments Since 2010. International Journal of Neonatal Screening. 2021;7.
17. Jansen ME, Metternick-Jones SC, Lister KJ. International differences in the evaluation of conditions for newborn bloodspot screening: a review of scientific literature and policy documents. European journal of human genetics : EJHG. 2016;25:10-6.
18. The University of Sheffield. Systematic reviews of screening for Severe Combined Immunodeficiency (SCID) in the NHS Newborn Blood Spot Screening Programme: Incidence, screening test characteristics and the effectiveness of treatments. 2017.
19. Cohen JF, Korevaar DA, Altman DG, Bruns DE, Gatsonis CA, Hooft L, et al. STARD 2015 guidelines for reporting diagnostic accuracy studies: explanation and elaboration. BMJ Open. 2016;6:e012799.
20. Campbell JM, Klugar M, Ding S, Carmody DP, Hakonsen SJ, Jadotte YT, et al. Diagnostic test accuracy: methods for systematic review and meta-analysis. JBI Evidence Implementation. 2015;13.
21. Kobrynski LJ. Newborn Screening in the Diagnosis of Primary Immunodeficiency. Clinical reviews in allergy & immunology. 2021.
22. Whiting PF, Rutjes AW, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Ann Intern Med. 2011;155:529-36.
23. Pai SY, Logan BR, Griffith LM, Buckley RH, Parrott RE, Dvorak CC, et al. Transplantation outcomes for severe combined immunodeficiency, 2000-2009. The New England journal of medicine. 2014;371:434-46.
24. Haddad E, Hoenig M. Hematopoietic Stem Cell Transplantation for Severe Combined Immunodeficiency (SCID). Frontiers in Pediatrics. 2019;7.
25. Castagnoli R, Delmonte OM, Calzoni E, Notarangelo LD. Hematopoietic Stem Cell Transplantation in Primary Immunodeficiency Diseases: Current Status and Future Perspectives. Frontiers in Pediatrics. 2019;7.
26. Patel NC, Chinen J, Rosenblatt HM, Hanson IC, Krance RA, Paul ME, et al. Outcomes of patients with severe combined immunodeficiency treated with hematopoietic stem cell transplantation with and without preconditioning. Journal of Allergy and Clinical Immunology. 2009;124:1062-9.e4.
27. Ylä-Herttuala S. ADA-SCID Gene Therapy Endorsed By European Medicines Agency For Marketing Authorization. Mol Ther. 2016;24:1013-4.
28. New gene therapy for the treatment of children with ultra-rare immune disorder recommended for approval [press release]. 2016.
29. European Medicines Agency. EU/3/05/313: Orphan designation for the treatment of severe combined immunodeficiency (SCID) due to adenosine deaminase (ADA) deficiency [Available from: https://www.ema.europa.eu/en/medicines/human/orphan-

designations/eu305313.
30. Health Service Executive. Treatment Abroad Scheme [Available from: https://www2.hse.ie/services/treatment-abroad-scheme/treatment-abroad-scheme.html.
31. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS medicine. 2009;6:e1000097.
32. Health Information and Quality Authority. Guidelines for Interpretation of Economic Evaluations 2014 [Available from: https://www.hiqa.ie/reports-and-publications/health-technology-assessments/guidelines-interpretation-economic.
33. van Mastrigt GA, Hiligsmann M, Arts JJ, Broos PH, Kleijnen J, Evers SM, et al. How to prepare a systematic review of economic evaluations for informing evidence-based healthcare decisions: a five-step approach (part 1/3). Expert review of pharmacoeconomics & outcomes research. 2016;16:689-704.
34. Mandrik O, Severens JL, Bardach A, Ghabri S, Hamel C, Mathes T, et al. Critical Appraisal of Systematic Reviews With Costs and Cost-Effectiveness Outcomes: An ISPOR Good Practices Task Force Report. Value in Health. 2021;24:463-72.
35. Evers S, Goossens M, De Vet H, Van Tulder M, Ament A. Criteria list for assessment of methodological quality of economic evaluations: Consensus on Health Economic Criteria. International journal of technology assessment in health care. 2005;21:240-5.
36. Caro JJ, Eddy DM, Kan H, Kaltz C, Patel B, Eldessouki R, et al. Questionnaire to assess relevance and credibility of modeling studies for informing health care decision making: an ISPOR-AMCP-NPC Good Practice Task Force report. Value in health. 2014;17:174-82.
37. Haute Authorité 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 2022 [Available from: https://www.has-sante.fr/jcms/p_3312418/en/evaluation-a-priori-de-l-extension-du-depistage-neonatal-au-deficit-immunitaire-combine-severe-par-la-technique-de-quantification-des-trecs-en-population-generale-en-france.
38. INESSS Quebec. Évaluation de la pertinence du dépistage néonatal du déficit immunitaire combiné sévère (SCID). 2022.
39. Husereau D, Drummond M, Petrou S, Carswell C, Moher D, Greenberg D, et al. Consolidated health economic evaluation reporting standards (CHEERS) statement. International journal of technology assessment in health care. 2013;29:117-22.
40. Department of Health. National Screening Advisory Committee: NSAC criteria 2020 [Available from: https://www.gov.ie/en/publication/c0d9f8-about-the-national-screening-advisory-committee/#nsac-criteria.

Appendix 1: NSAC criteria by HTA domain

Criterion No.	NSAC Grouping	Criterion	HTA domain(s)*
1	The Condition	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.	Epidemiology
2		All the cost-effective primary prevention interventions should have been implemented as far as practicable.	Not applicable**
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.	Epidemiology, *Ethical, social and legal issues*
4	The Screening Method	The screening method should be, as far as is practicable: a) simple b) safe c) precise d) reliable e) validated.	Clinical effectiveness and safety, *Organisational issues*
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.	Description of technology, Clinical effectiveness and safety, *Organisational issues*
6		The screening process should be acceptable to the target population.	*Ethical, social and legal issues*
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.	Description of technology, *Organisational issues*
8		If screening is for a particular mutation(s) or set of genetic variants, the method for their selection should be kept under review.	*Organisational issues*
9	The Intervention	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.	Description of technology, Clinical effectiveness and safety
10		There should be agreed evidence-based policies covering which individuals should be offered interventions and the appropriate intervention to be offered.	Description of technology, *Organisational issues*
11	The Screening Programme	Ideally there should be evidence from high quality randomised controlled trials that the screening programme is effective in reducing mortality or morbidity. Where	Clinical effectiveness and safety, *Ethical, social and legal issues*

Criterion No.	NSAC Grouping	Criterion	HTA domain(s)*
		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.	*Ethical, social and legal issues, Organisational issues*
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.	*Ethical, social and legal issues, Organisational issues*
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.	*Economic analysis*
15	Implementation Criteria	Clinical management of the condition and patient outcomes should be in place before a screening programme is initiated.	*Organisational issues*
16		Adequate staffing and facilities for testing, diagnosis, treatment and programme management should be available prior to the commencement of the screening programme.	*Organisational issues*
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.	*Economic analysis*, *Ethical, social and legal issues*
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 sub-groupings in the population.	*Organisational issues*
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.	*Ethical, social and legal issues, Organisational issues*

Criterion No.	NSAC Grouping	Criterion	HTA domain(s)*
20		Decisions about commencing, expanding or ceasing a programme should be based on scientifically validated evidence.	All

Key: HTA – health technology assessment; NSAC – National Screening Advisory Committee.
Source of NSAC criteria: Department of Health[40]
Note: HTA domains in italics are conducted as part phase 2 of the HTA, which will only proceed as per Figure 1.
* A mapping exercise was conducted by the HIQA evaluation team to identify the relevant HTA domain for each of the individual NSAC criteria, based on the HTA Core Model® proposed by the European Network for Health Technology Assessment (EUnetHTA).[12] The mapping exercise aimed to clarify the extent to which a typical HTA addresses the NSAC criteria, and which HTA domain addresses which criterion/criteria.
** Considered outside the scope of a conventional HTA, unless the HTA is undertaken specifically to inform this criterion.

Appendix 2: Provisional search strategies

Search 1: Test accuracy of TREC for SCID

Medline (EBSCO, 28 October 2021)		
#	**Query**	**Results**
S18	S17 Limiters - Date of Publication: 20100101-20211231 Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	216
S17	S11 AND S15 AND S16	228
S16	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8	70,547
S15	S12 OR S13 OR S14	6,724
S14	AB ((dried OR dry) N1 (blood spot OR blood test* OR blood sampl*)) OR TI ((dried OR dry) N1 (blood spot OR blood test* OR blood sampl*))	5,375
S13	(MH "Dried Blood Spot Testing")	1,750
S12	AB ("T cell receptor excision circle*" or "T-cell receptor excision circle*" or TREC or TRECs) OR TI ("T cell receptor excision circle*" or "T-cell receptor excision circle*" or TREC or TRECs)	1,053
S11	S9 OR S10	19,044
S10	(MH "Neonatal Screening")	10,889
S9	S12 TI ((newborn or "newly born" or neonat* or infant) N3 screen*) OR AB ((newborn or "newly born" or neonat* or infant) N3 screen*)	13,860
S8	(MH "X-Linked Combined Immunodeficiency Diseases")	243
S7	(MH "Primary Immunodeficiency Diseases+")	13,724
S6	(MH "Severe Combined Immunodeficiency+")	4,216
S5	AB ("b-cell lymphopenia*" or "b cell lymphopenia*") OR TI ("b-cell lymphopenia*" or "b cell lymphopenia*")	115
S4	AB ("t cell lymphopenia*" or "t-cell lymphopenia*") OR TI ("t cell lymphopenia*" or "t-cell lymphopenia*")	434
S3	AB ("X linked" or "X-linked") OR TI ("X linked" or "X-linked")	30,839
S2	AB (PID or PIDs OR "primary immunodeficienc*" or "primary immune deficienc*") OR TI (PID OR PIDs OR"primary immunodeficienc*" or "primary immune deficienc*")	9,911
S1	AB (SCID OR SCIDs OR "severe combined immunodeficiency" or "severe combined immunologic* deficiency" or "combined immunodeficienc*" or "severe combined immunodeficiency syndrome") OR TI (SCID OR SCIDs OR "severe combined immunodeficiency" or "severe combined immunologic* deficiency" or "combined immunodeficienc*" or "severe combined immunodeficiency syndrome")	

Embase (Ovid, 28 October 2021)		
#	**Searches**	**Results**
1	(SCID or SCIDs or severe combined immunodeficienc* or severe combined immune deficienc* or severe combined immunologic* deficienc* or combined immunodeficienc*).ab,ti.	37109
2	(primary immune deficienc* or primary immunodeficienc* or PID or PIDs).ab,ti.	16507
3	(X Linked or X-linked).ab,ti.	41128
4	exp severe combined immunodeficiency/	6700
5	exp immune deficiency/	303667
6	(t cell lymphopenia* or t-cell lymphopenia*).ab,ti.	799
7	(b-cell lymphopenia* or b cell lymphopenia*).ab,ti.	256
8	((newborn or newly born or neonat* or infant) adj3 Screening*).ab,ti.	18927
9	exp newborn screening/	20457
10	(T-cell receptor excision circle* or T cell receptor excision circle* TREC or TRECs).ab,ti.	1154
11	exp t-cell receptor excision circle test kit/	7
12	exp dried blood spot testing/	4656
13	((dried or dry) adj1 (blood spot or blood test* or blood sampl*)).ab,ti.	1448
14	8 or 9	25826
15	10 or 11 or 12 or 13	6689
16	1 or 2 or 3 or 4 or 5 or 6 or 7	373742
17	8 or 9	25826
18	15 and 16 and 17	424
19	limit 18 to yr="2010 -Current"	413

Cochrane Library (1 November 2021)		
#	**Search**	**Results**
1.	(SCID or SCIDs or severe combined immunodeficienc* or severe combined immune deficienc* or severe combined immunologic* deficienc* or combined immunodeficienc*):ti,ab,kw (Word variations have been searched)	5098
2.	(primary immune deficienc* or primary immunodeficienc* or PID or PIDs):ti,ab,kw (Word variations have been searched)	5338
3.	(X Linked or X-linked):ti,ab,kw (Word variations have been searched)	2186
4.	MeSH descriptor: [Severe Combined Immunodeficiency] explode all trees	5

5.	(t cell lymphopenia* or t-cell lymphopenia*):ti,ab,kw (Word variations have been searched)	11772
6.	(b-cell lymphopenia* or b cell lymphopenia*):ti,ab,kw (Word variations have been searched)	133
7.	#1 OR #2 OR #3 OR #4 OR #5 OR #6	22374
8.	((newborn or newly born or neonat* or infant) NEAR/3 Screening*):ti,ab,kw (Word variations have been searched)	606
9.	MeSH descriptor: [Neonatal Screening] explode all trees	135
10.	(T-cell receptor excision circle* or T cell receptor excision circle* TREC or TRECs):ti,ab,kw (Word variations have been searched)	101
11.	((dried or dry) NEAR/1 (blood spot or blood test* or blood sampl*)):ti,ab,kw (Word variations have been searched)	495
12.	MeSH descriptor: [Dried Blood Spot Testing] explode all trees	27
13.	#8 OR #9	606
14.	#10 OR #11 OR #12	595
15.	#7 AND #13 AND #14	5

Search 2: Benefits of early treatment

Medline (EBSCO, 2 November 2021)		
#	**Searches**	**Results**
S1	(MH "Severe Combined Immunodeficiency+")	4,234
S2	(MH "X-Linked Combined Immunodeficiency Diseases")	246
S3	AB ("severe combined immunodeficiency" or "severe combined immunologic* deficiency" or "combined immunodeficienc*" or "severe combined immunodeficiency syndrome" or SCID or SCIDs) OR TI ("severe combined immunodeficiency" or "severe combined immunologic* deficiency" or "combined immunodeficienc*" or "severe combined immunodeficiency syndrome" or SCID or SCIDs)	21,335
S4	TI ("X-linked" or "X linked") OR AB ("X-linked" or "X linked")	30,953
S5	TI ("t cell lymphopenia*" or "t-cell lymphopenia*" or "b cell lymphopenia*" or "b-cell lymphopenia*") OR AB ("t cell lymphopenia*" or "t-cell lymphopenia*" or "b cell lymphopenia*" or "b-cell lymphopenia*")	550
S6	TI (PID or PIDs or "primary immunodeficienc*" or "primary immune deficienc*" or "congenital immunodeficienc*") OR AB (PID or PIDs or "primary immunodeficienc*" or "primary immune deficienc*" or "congenital immunodeficienc*")	10,239
S7	S1 OR S2 OR S3 OR S4 OR S5 OR S6	62,694
S8	(MH "Hematopoietic Stem Cell Transplantation+")	50,536
S9	(MH "Stem Cell Transplantation+")	90,484
S10	(MH "Bone Marrow Transplantation")	45,153
S11	TI "hematopoietic stem cell transplant*" OR "haematopoietic stem cell transplant*" OR AB "hematopoietic stem cell transplant*" OR "haematopoietic stem cell transplant*"	26,264
S12	AB "stem cell transplant*" OR TI "stem cell transplant*"	52,250
S13	TI "bone marrow transplant*" OR AB "bone marrow transplant*"	32,568
S14	S8 OR S9 OR S10 OR S11 OR S12 OR S13	154,329
S15	S7 AND S14	4,272
S16	(MH "Infant, Newborn+")	637,628
S17	TI (newborn* or "new born" or "newly born" or infant* or neonate*) OR AB (newborn* or "new born" or "newly born" or infant* or neonate*)	586,282
S18	S16 OR S17	945,250
S19	S15 AND S18	731
S20	(MH "Mass Screening+")	136,380
S21	(MH "Early Diagnosis+")	59,052
S22	TI (screening or "early detection" or "early diagnosis") OR AB (screening or "early detection" or "early diagnosis")	713,430
S23	S20 OR S21 OR S22	777,683
S24	S19 AND S23	190

Embase (Ovid, 02 November 2021)		
#	**Searches**	**Results**
1	(H?ematopoietic Stem Cell Transplant* or H?ematopoietic Stem-Cell Transplant* or H?ematopoietic Stem-Cell therapy or H?ematopoietic Stem Cell therapy).ab,ti.	49130

2	"Bone Marrow Transplant*".ab,ti.	44101
3	"Stem Cell Transplant*".ab,ti.	102532
4	exp bone marrow transplantation/ or exp stem cell transplantation/	226567
5	exp hematopoietic stem cell transplantation/	75217
6	(SCID or SCIDs or severe combined immunodeficiency or severe combined immunologic* deficiency or combined immunodeficienc* or severe combined immunodeficiency syndrome or congenital deficienc*).ab,ti.	38023
7	(PID or PIDs or primary immunodeficienc*or primary immune deficienc*).ab,ti.	8636
8	(x linked or x-linked).ab,ti.	41165
9	(t cell lymphopenia* or t-cell lymphopenia* or b cell lymphopenia* or b-cell lymphopenia*).ab,ti.	1028
10	exp combined immunodeficiency/ or exp severe combined immunodeficiency/ or exp immune deficiency/	303859
11	exp mass screening/	268668
12	exp early diagnosis/	115599
13	(screening or early diagnosis or early detection).ab,ti.	1000523
14	(newborn or new born or newly born or neonat* or infant).ab,ti.	333624
15	exp newborn/	556451
16	1 or 2 or 3 or 4 or 5	250920
17	6 or 7 or 8 or 9 or 10	374305
18	11 or 12 or 13	1155587
19	14 or 15	752902
20	16 and 17 and 18 and 19	447

Cochrane library (3 November 2021)		
#	**Searches**	**Results**
1.	(SCID or SCIDs or severe combined immunodeficienc* or severe combined immune deficienc* or severe combined immunologic* deficienc* or combined immunodeficienc*):ti,ab,kw (Word variations have been searched)	5098
2.	(primary immune deficienc* or primary immunodeficienc* or PID or PIDs):ti,ab,kw (Word variations have been searched)	5338
3.	(X Linked or X-linked):ti,ab,kw (Word variations have been searched)	2186
4.	MeSH descriptor: [Severe Combined Immunodeficiency] explode all trees	5
5.	(t cell lymphopenia* or t-cell lymphopenia*):ti,ab,kw (Word variations have been searched)	11772
6.	(b-cell lymphopenia* or b cell lymphopenia*):ti,ab,kw (Word variations have been searched)	133
7.	#1 OR #2 OR #3 OR #4 OR #5 OR #6	22374
8.	(newborn or newly born or neonat* or infant):ti,ab,kw (Word variations have been searched)	77139
9.	MeSH descriptor: [Infant, Newborn] explode all trees	16851
10.	(screening or "early detection" or "early diagnosis"):ti,ab,kw (Word variations have been searched)	84046
11.	MeSH descriptor: [Mass Screening] explode all trees	3968
12.	#8 OR #9	77139
13.	#10 OR #11	84381

14.	("hematopoietic stem cell transplant*" OR "haematopoietic stem cell transplant*" OR "hematopoietic stem-cell transplant*" OR "haematopoietic stem-cell transplant*"):ti,ab,kw (Word variations have been searched)	3875
15.	MeSH descriptor: [Hematopoietic Stem Cell Transplantation] explode all trees	1477
16.	("bone marrow transplant*" OR "stem cell transplant*"):ti,ab,kw (Word variations have been searched)	11489
17.	MeSH descriptor: [Bone Marrow Transplantation] explode all trees	1390
18.	#14 OR #15 OR #16 OR #17	11489
19.	#7 AND #12 AND #13 AND #18	2

Search 3: Cost effectiveness of newborn screening for SCID

EMBASE		
#	**Searches (EMBASE)**	**Results**
1	(SCID or SCIDs or severe combined immunodeficienc* or severe combined immune deficienc* or severe combined immunologic* deficienc* or combined immunodeficienc*).ab,ti.	22745
2	(primary immune deficienc* or primary immunodeficienc* or PID or PIDs).ab,ti.	10861
3	(X Linked or X-linked).ab,ti.	31937
4	exp severe combined immunodeficiency/	4373
5	immune deficiency/	1131
6	(t cell lymphopenia* or t-cell lymphopenia*).ab,ti.	465
7	(b-cell lymphopenia* or b cell lymphopenia*).ab,ti.	126
8	((newborn or newly born or neonat* or infant) adj3 Screening*).ab,ti.	13094
9	exp newborn screening/	11455
10	(T-cell receptor excision circle* or T cell receptor excision circle* TREC or TRECs).ab,ti.	703
11	exp dried blood spot testing/	1961
12	((dried blood or dry blood) adj1 (spot or test* or sampl*)).ab,ti.	2811
13	Dried Blood Spot Testing/	1961
14	Early Diagnosis/	29670
15	guthrie.ab,ti.	789
16	'heel prick'.ab,ti.	356
17	(early detection or early diagnosis).ab,ti.	162705
18	1 or 2 or 3 or 4 or 5 or 6 or 7	66184
19	8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17	198684
20	(cost* or cost benefit analys* or health care costs).mp.	815566

21	18 and 19 and 20	89

MEDLINE		
#	**Query**	**Results**
S21	S18 AND S19 AND S20	90
S20	AB cost* OR TI cost* OR (MH "Costs and Cost Analysis+") OR AB "cost benefit analys*" OR TI "cost benefit analys*" OR (MH "Cost-Benefit Analysis") OR (MH "Health Care Costs+")	818,657
S19	S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17	202,993
S18	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8	72,979
S17	AB ("early diagnosis" OR "early detection") OR TI ("early diagnosis" OR "early detection")	162,182
S16	(MH "Neonatal Screening")	11,394
S15	(MH "Early Diagnosis")	29,575
S14	(MH "Dried Blood Spot Testing")	1,930
S13	AB (dried blood OR dry blood) N1 (spot OR test* OR sampl*)) OR TI (dried blood OR dry blood) N1 (spot OR test* OR sampl*))	5,656
S12	AB heel prick OR TI heel prick	373
S11	AB guthrie OR TI guthrie	849
S10	AB ("T cell receptor excision circle*" or "T-cell receptor excision circle*" or TREC or TRECs) OR TI ("T cell receptor excision circle*" or "T-cell receptor excision circle*" or TREC or TRECs)	1,114
S9	TI ((newborn or "newly born" or neonat* or infant) N3 screen*) OR AB ((newborn or "newly born" or neonat* or infant) N3 screen*)	17,037
S8	(MH "X-Linked Combined Immunodeficiency Diseases")	258
S7	(MH "Primary Immunodeficiency Diseases+")	14,467
S6	(MH "Severe Combined Immunodeficiency+")	4,356
S5	AB ("b-cell lymphopenia*" or "b cell lymphopenia*") OR TI ("b-cell lymphopenia*" or "b cell lymphopenia*")	124
S4	AB ("t cell lymphopenia*" or "t-cell lymphopenia*") OR TI ("t cell lymphopenia*" or "t-cell lymphopenia*")	464
S3	AB ("X linked" or "X-linked") OR TI ("X linked" or "X-linked")	31,858
S2	AB (PID or PIDs OR "primary immunodeficienc*" or "primary immune deficienc*") OR TI (PID OR PIDs OR "primary immunodeficienc*" or "primary immune deficienc*")	10,401
S1	AB (SCID OR SCIDs OR "severe combined immunodeficienc*" or "severe combined immunologic* deficienc*" or "combined immunodeficienc*" or "severe combined immunodeficiency syndrome")OR TI (SCID OR SCIDs OR "severe combined immunodeficiency" or "severe combined immunologic* deficienc*" or "combined immunodeficienc*" or "severe combined immunodeficiency syndrome")	21,797

The Cochrane Library		
#1	(SCID or SCIDs or severe combined immunodeficienc* or severe combined immune deficienc* or severe combined immunologic* deficienc* or combined immunodeficienc*):ti,ab,kw	1979
#2	(primary immune deficienc* or primary immunodeficienc* or PID or PIDs):ti,ab,kw	5402
#3	(X Linked or X-linked):ti,ab,kw	1715
#4	(t cell lymphopenia* or t-cell lymphopenia*):ti,ab,kw	9201
#5	(b-cell lymphopenia* or b cell lymphopenia*):ti,ab,kw	125
#6	MeSH descriptor: [] explode all trees	0
#7	MeSH descriptor: [X-Linked Combined Immunodeficiency Diseases] explode all trees	1

#8	MeSH descriptor: [Severe Combined Immunodeficiency] explode all trees	6
#9	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8	17536
#10	((newborn or newly born or neonat* or infant) NEAR/3 Screening*):ti,ab,kw	629
#11	((dried blood or dry blood) NEAR/1 (spot or test* or sampl*)):ti,ab,kw	47175
#12	("Guthrie"):ti,ab,kw (Word variations have been searched)	39
#13	("heel prick"):ti,ab,kw (Word variations have been searched)	152
#14	("early detection OR early diagnosis"):ti,ab,kw (Word variations have been searched)	0
#15	MeSH descriptor: [Early Diagnosis] this term only	564
#16	MeSH descriptor: [Dried Blood Spot Testing] explode all trees	30
#17	#10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16	48383
#18	#9 AND #17	996
#19	(cost* OR "cost benefit analys*"):ti,ab,kw (Word variations have been searched)	79593
#20	MeSH descriptor: [] explode all trees	0
#21	MeSH descriptor: [Cost-Benefit Analysis] explode all trees	7704
#22	MeSH descriptor: [Health Care Costs] explode all trees	3588
#23	#19 OR #20 OR #21 OR #22	79593
#24	#18 AND #23	52

Grey literature search

The below list of electronic sources will be searched using key words (such as "newborn screening", "TREC", "SCID" and "HSCT"):

- Centers for Disease Control and Prevention; Available from https://www.cdc.gov/newbornscreening/index.html
- Cochrane Register of Diagnostic Test Accuracy Studies; Available from https://methods.cochrane.org/sdt/cochrane-diagnostic-test-accuracy-reviews
- European Centre for Disease Prevention and Control; Available from https://www.ecdc.europa.eu/en
- Google Scholar and Google; Available from https://scholar.google.com/, https://www.google.ie
- HTAi vortal; Available from https://www.htai.org/index.php?id=579
- National Coordinating Centre for Health Technology Assessment (NCCHTA); Available from https://www.nihr.ac.uk/funding-and-support/funding-for-research-studies/funding-programmes/health-technology-assessment/
- Web of Science; Available from https://libguides.rcsi.ie/WOS
- World Health Organization (WHO); Available from http://www.who.int/en/

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