Health Information and Quality Authority

An tÚdarás Um Fhaisnéis agus Cáilíocht Sláinte

Health technology assessment of the addition of spinal muscular atrophy (SMA) to the National Newborn Bloodspot Screening Programme

Published: 27 November 2023

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.

Table of contents

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.

Spinal muscular atrophy (SMA) is a rare genetic neuromuscular disorder. The severity of SMA varies. However, it is characterised by irreversible degeneration of motor neurons in the spinal cord resulting in progressive muscle wasting and weakness. While this condition was historically associated with supportive care only, a number of disease-modifying treatments are now approved for use in the European Union. Newborn bloodspot screening for SMA is possible and has the potential to enable earlier identification and diagnosis, 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.

Dr Máirín Ryan

Deputy Chief Executive and Director of Health Technology Assessment

Acknowledgements

HIQA would like to thank all of the individuals and organisations who provided their time, advice and information in support of this report including Professor Sinéad Murphy, consultant neurologist at Tallaght University Hospital, and Fionn McCarthy, statistician at the HSE Healthcare Pricing Office. Particular thanks are due to the members of the Expert Advisory Group (EAG) below who provided advice and information.

HIQA further notes that membership of the EAG involves review of evidence synthesis documents and contribution to a discussion which informs the advice from HIQA to NSAC. It does not necessarily imply agreement with all aspects of the evidence synthesis or the subsequent advice.

The membership of the EAG was as follows:

Dr Aileen Butler	Principal Clinical Scientist, Molecular Genetics Laboratory, Children's Health Ireland (CHI) at Crumlin
Dr Abigail Collins	National Clinical Lead, Child Health, Public Health
Dr David Elliman	Chair, Blood Spot Task Group, United Kingdom
Dr Mohamed Elsammak	Director and Consultant Chemical Pathologist, National Newborn Bloodspot Screening Laboratory, Children's Health Ireland at Temple Street
Sinéad Lucey **Dr Claire Gorry (alternate)**	Chief II Pharmacist, Medicines Management Programme, HSE Chief I Pharmacist, Medicines Management Programme, HSE
Professor Andrew Green	Consultant in Clinical Genetics and Professor of Medical Genetics, Children's Health Ireland at Crumlin *Nominated by:* Royal College of Physicians of Ireland
Catherine Harvey	Clinical Liaison Officer, Newborn Bloodspot Screening Laboratory, Children's Health Ireland at Temple Street
Sue Jameson	Cuidiú

Sinéad Lawlor **Grainne Ryan (alternate)**	National Practice Development Co-Ordinator (Public Health Nursing Service), Office of Nursing and Midwifery Services Director, HSE National Lead for Public Health Nursing service, HSE
Paul Marsden	Project Manager for Child Health Screening Programmes, HSE
Professor Denise McDonald	Consultant in paediatric neurodisability, Children's Health Ireland at Tallaght *Nominated by:* National Clinical Programme for Paediatrics and Neonatology
Ellen McGrath	Head of Corporate Pharmaceutical Unit, Primary Care Eligibility & Reimbursement Service, HSE
Professor John Murphy	Clinical Lead for Neonatology, National Clinical Programme for Paediatrics and Neonatology *Nominated by:* HSE National Women and Infants Health Programme
Dr Margaret O'Brien	Consultant Neurologist, Beaumont Hospital *Nominated by:* National Clinical Programme for Neurology
Jonathan O'Grady	Director, SMA Ireland
Loretta O'Grady	Chief Medical Scientist, Newborn Bloodspot Screening Laboratory, Children's Health Ireland (CHI) at Temple Street
Dr Declan O'Rourke	Consultant Paediatric Neurologist, Children's Health Ireland at Temple Street *Nominated by:* National Clinical Programme for Paediatrics and Neonatology
Evette Wade^ **Inese Freimane (alternate for Evette Wade)**	Population Health Screening Unit, Department of Health
Joanne Uí Chrualaoich	Principal Officer, Population Health Screening Unit, Department of Health
Dr Alana Ward	Information Scientist, National Rare Diseases Office
Dr Patricia Harrington	Deputy Director of HTA, Health Information and Quality Authority

Dr Máirín Ryan (Chair)	Director of HTA and Deputy Chief Executive Officer, Health Information and Quality Authority
Dr Susan Spillane	Deputy Director of HTA, Health Information and Quality Authority

^ Left EAG prior to second meeting

This report was led by staff in HIQA's HTA Directorate. The following individuals contributed to the management, technical writing or dissemination of this report:

Helen O'Donnell (project lead*), Laura Comber (former project lead*), Marie Carrigan, Sarah Dillon, Éanán Finnegan, Patricia Harrington, Karen Jordan, Louise Larkin, Arielle Maher, Michelle O'Neill, Michelle O'Shea, Máirín Ryan, Debra Spillane, Susan Spillane, Conor Teljeur.

* Laura Comber left HIQA in July 2023, at which point Helen O'Donnell assumed the project lead role.

Funding

A member of the evaluation team, Sarah Dillon, was supported by the Irish Health Research Board and the HSC Public Health Agency (Grant number CBES-2018-001) in association with Evidence Synthesis Ireland/Cochrane Ireland.

Conflicts of interest

Jonathan O'Grady is a Director of SMA Ireland. SMA Ireland is a registered charity which represents people and families affected by SMA. The charity has received funding from pharmaceutical companies which produce treatments for SMA. In the latest annual audited accounts to 31 December 2022, 91% of SMA Ireland's total income was received from Novartis Ireland. This was to fund a newborn screening advocacy event held in December 2022.

Dr Declan O'Rourke has received funding from Novartis for participation as a steering group member for a peer-to-peer educational forum on gene therapies.

Key findings and Advice to the NSAC

In January 2023, 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 screening for spinal muscular atrophy (SMA) to the National Newborn Bloodspot Screening Programme (NNBSP) in Ireland.

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

- SMA is a rare, but serious genetic neuromuscular disorder caused by a pathogenic variant in the survival motor neuron 1 (*SMN1*) gene and is associated with irreversible motor neuron loss and disease progression.
    - In recent years, the availability of disease-modifying therapies has significantly improved prognosis, particularly when initiated early in the disease course.
    - In the absence of disease-modifying treatment, the natural history of SMA is broadly characterised by progressive motor and respiratory muscle wasting and weakness of varying severity. In most cases, this results in motor milestones not being reached (for example, sitting, walking), problems with breathing or swallowing (requiring mechanical ventilation in severe cases), and frequent respiratory infections.
    - This loss of the functional *SMN1* gene can be partially compensated for by the presence of another gene, survival motor neuron 2 (*SMN2*). *SMN2* can be considered a disease-modifying gene, since, typically, as *SMN2* copy number increases, the severity of the disease course decreases. However, this correlation is not absolute.
- SMA is categorised into five distinct clinical subtypes (type 0 to type IV) based on age of symptom onset and maximum motor function achieved. Symptoms may present at birth (type 0), shortly after birth (type I), during childhood (type II and III) or in adulthood (type IV). Younger age at onset is associated with more severe disease; type 0 which has onset in utero is associated with early infant mortality.
- Under current practice, the proportions of SMA cases that present as types I to IV were estimated through a meta-analysis of identified studies. Type I compromised 55.3% of cases, with type II representing 23.3%, type III 20.4%, and type IV 1.0%.
- In Ireland, cases of SMA are currently identified by family history or through clinical presentation. Cases presenting clinically with symptoms have already experienced irreversible loss of motor neurons. In the absence of screening, it is possible that some cases are not identified, for example, those who

experience very early mortality and those who experience a very mild disease course.

- Irish SMA case data were provided by Children's Health Ireland (CHI) at Temple Street; information on age at diagnosis was available for 25 paediatric cases presenting between 2015 and 2022. The median ages at diagnosis for types I-III SMA were as follows: type I, six months (range 0 to 7.9 months); type II, 19 months (range 12 to 24 months); type III, 144 months (range 42 to 192 months).
- Newborn bloodspot screening for SMA uses polymerase chain reaction-based methods to detect homozygous deletions of *SMN1* (that is, deletions affecting both copies of the *SMN1* gene).
    - Samples which return a screen positive result for *SMN1* deletion typically undergo confirmatory testing to confirm *SMN1* deletions and to quantify *SMN2* copy number in order to inform prognosis and treatment planning. It may be possible to perform confirmatory testing on the original bloodspot sample taken for the purpose of newborn screening. If this is the case, this would mean that there would be no need to contact the family for a separate blood draw, thereby minimising the impact of a false positive screening result on them. The need for a separate blood draw would however depend on the outcomes of the laboratory verification process (that is, the phase in which the testing method is established, which occurs prior to implementing screening in the population).
    - The proposed screening test will not identify those with compound heterozygous variants of *SMN1* (2 to 5% of SMA cases, where a deletion occurs in one copy of the gene and a point mutation in the other).
- International practice, in terms of newborn bloodspot screening for SMA, has undergone substantial change in recent years. HIQA's review of screening practice in 34 counties identified that newborn bloodspot screening is fully implemented at a national level in eight countries, implemented at a regional level in four countries, under implementation in one country, being piloted in seven countries, and is under review in two further countries.
- Estimates of incidence vary internationally. Data suggest an average of 6.5 cases (95% prediction interval (PI): 2.4 to 13.2) of types I to IV SMA a year in Ireland based on approximately 58,000 births.
- The majority of SMA cases identified through screening have not yet developed symptoms. Therefore, introduction of screening effectively removes clinical subtyping; decisions on prognosis and treatment instead rely

on genetic phenotype using the patient's *SMN2* gene copy number as a biomarker.

- A meta-analysis was undertaken to indicate the likely clinical course for individuals based on *SMN2* copy number. This was conducted using historical data from patients presenting clinically with symptoms. Of identified patients:
    - 85.0% (95% CI: 65.3% to 94.5%) were estimated to have up to three copies of *SMN2*. Of these, 99.8% (95% CI: 98.8% to 100%) were estimated to present with types I to III SMA.
    - 11.1% (95% CI: 4.3% to 19.9%) were estimated to have four copies of *SMN2*. Of these, 94.4% (95% CI: 82.8% to 99.2%) were estimated to present with types I to III, with the remainder presenting with type IV SMA (5.6%, 95% CI: 0.8% to 17.2%).
    - 3.9% (95% CI: 0.0% to 22.8%) were estimated to have five or more copies of *SMN2*. The likely SMA type in this cohort is subject to substantial uncertainty due to the very small number of cases with five or more copies that have presented clinically in the absence of screening. However, the available evidence suggests that these patients would likely have milder disease types.
    - As identification was primarily based on symptomatic presentation, the percentages of patients with higher copy numbers may be underestimated. This is because these individuals typically experience a milder disease course and may be less likely to present in clinical practice.
- A systematic review of newborn screening programmes for SMA was undertaken with the primary outcome of interest being clinical effectiveness. Thirty-two relevant publications, describing 20 unique studies, were included.
    - In 16 studies, screening for SMA was reported to accurately detect homozygous deletions on exon 7 of the *SMN1* gene (the location of interest for identification of SMA).
    - Referrals for confirmatory testing as a percentage of the total population screened ranged from <0.01% to 0.14% with the midpoint across all studies being 0.01% (1 in 10,000 screened).
    - As a percentage of the total population screened, the false positivity rate was estimated at less than 0.01% (less than 1 in 10,000) in all but one study (0.12%). Based on pooled data across the 16 studies which reported false positivity rates, the ratio of SMA cases to false positives detected was 6:1.
    - Considering total referrals and the false positivity rate, the international evidence suggests no substantial relative increase in the diagnosed incidence after the introduction of screening. However, the impact of

screening on the diagnosed incidence cannot be accurately assessed given the recent introduction of international screening programmes.
    - Collectively, of approximately 3.2 million infants screened, 240 cases of SMA were identified through screening. Of these, 49% (n = 118) had two copies of *SMN2*, 30% (n = 71) had three and 13% (n = 31) had four copies. Several of the studies combined data for those with four or more copies; these cases are not included in these estimates, so the percentage specifically with four copies is an underestimate. Of note, 32% of identified cases were noted to be symptomatic prior to treatment beginning.
    - One non-randomised study from Australia compared clinical outcomes in screened and unscreened cohorts. For identified cases (screened n=15; unscreened n=18) there was evidence to suggest screening was associated with improved functional outcomes. Of note, only one case in each cohort had four or more *SMN2* copies.
    - The evidence relating to clinical outcomes of a screening programme for SMA is inherently linked to the clinical outcomes of the disease-modifying treatments. Therefore, the impact of the screening programme in isolation is difficult to confirm.
- There is currently no known cure for SMA. However, treatments are available to increase production of functional SMN protein. The first drug was licensed by the European Medicines Agency (EMA) in 2017. As of September 2023, three drugs have now been licensed: nusinersen (Spinraza®), onasemnogene abeparvovec (Zolgensma®) and risdiplam (Evrysdi®).
    - These drugs differ in their licensed indications and in their reimbursement by the HSE.
    - These drugs are associated with very high drug acquisition costs. Annual costs to the HSE based on the list price were estimated as approximately €255,000 per patient for each of nusinersen and risdiplam and €2.2 million per patient for onasemnogene abeparvovec when administered as a one-off treatment. The actual costs to the HSE are anticipated to be lower, but this cannot be confirmed due to the confidential nature of the agreements.
    - Current reimbursement criteria were agreed in the absence of a screening programme. Funding arrangements would need to be clarified for those that would be identified through screening.
- An overview of treatment effectiveness was undertaken.
    - Based on limited data, there is evidence that treatment with these drugs leads to improved outcomes in individuals who have developed symptoms compared to no treatment. The evidence (primarily in type I

disease) also suggests that earlier treatment is more beneficial than later treatment.
    - Less evidence is available for presymptomatic patients, with data limited to those with two or three copies of *SMN2* only; these data suggest that earlier intervention is associated with improved clinical outcomes.
    - Follow-up data are limited, therefore, there is substantial uncertainty regarding the long-term effectiveness of these drugs.
- The introduction of screening for SMA would change treatment pathways for children with SMA. Some cases may receive a different treatment than they would have received if they had presented symptomatically at a later point. Additionally, a small number of cases who would have remained unidentified for many years may receive early treatment or be managed with a watchful waiting strategy, where their condition is monitored for evidence of disease progression before treatment begins.
- A systematic review was undertaken of the international evidence on the cost effectiveness of newborn bloodspot screening for SMA compared with clinical presentation. Changes in the therapeutic landscape and variation in methodological approaches contributed to a wide range of results across the four cost-utility analyses (CUAs) and one cost-effectiveness analysis identified.
    - Newborn bloodspot screening for SMA was considered cost saving in two of the four identified CUAs. It was considered not cost effective (adjusted incremental cost-effectiveness ratio (ICER) €231,004 per quality-adjusted life year (QALY)) at a willingness-to-pay threshold of €45,000 per QALY gained in one CUA, while in the fourth CUA, the ICER varied between not cost effective (€307,746 per QALY) and cost saving depending on the treatment strategy.
    - In general, studies were considered to be of low to moderate quality largely due to limitations in the evidence base and inadequate reporting. Conflicts of interest arising from relationships with pharmaceutical companies were reported in three out of the five included studies. None of the studies were considered directly applicable to the Irish context.
    - De novo modelling to inform cost effectiveness of screening in the Irish setting was not undertaken given insufficient evidence to inform reliable estimation of the cost effectiveness of screening in the Irish setting. This included limited comparative data for screened versus non-screened populations, an absence of long-term clinical effectiveness data, and a lack of evidence for those with higher *SMN2* copy numbers.

- In 2023, it was agreed that the NNBSP should be expanded to include screening for severe combined immunodeficiency (SCID). Multiplex assays are available to screen for both SCID and SMA at the same time. Should screening for SMA be recommended, this would potentially result in operational efficiencies in terms of the equipment requirements, physical space requirements, training needs of staff, and verification and screening processes, as compared to a scenario where SMA were to be introduced in the absence of screening for SCID.
- A budget impact analysis was undertaken to estimate the incremental budget impact associated with the addition of screening for SMA to the NNBSP relative to identification based on clinical suspicion or family history (current care).
    - The incremental budget impact (that is, the budget impact over and above current expenditure in the absence of screening), was estimated at approximately €17.7 million (95% confidence interval (CI): €5.1 to €40.5 million) over a five-year time horizon.
    - Total laboratory costs, comprising equipment and consumables associated with screening, were estimated as representing less than 5% of costs (€0.7 million, 95% CI: €0.6 to €0.8). The costs of scheduled healthcare utilisation (€0.1 million, 95% CI: €0.02 to €0.3) and clinical staff (€0.5 million, 95% CI: €0.4 to €0.7) also comprised a small proportion of the total incremental budget impact (< 5%).
    - The incremental budget impact was largely (approximately 90%) driven by the cost of disease-modifying therapies (€16.3 million, 95% CI: €3.8 to €38.9). This was primarily accounted for by changes to the treatments that would be received by individuals under screening. Specifically, more individuals were modelled as receiving one-off treatment with onasemnogene abeparvovec than would receive it under current care. Without screening, these cases would commence treatment at symptom onset with nusinersen or risdiplam for an indefinite duration. As onasemnogene abeparvovec is associated with a very high upfront cost, its contribution to the overall budget impact is particularly observed over shorter time horizons (such as the five years modelled). However, use of a longer time horizon would be subject to even greater uncertainty given the evolving treatment landscape.
    - Drug costs were calculated based on the publicly known list price. It is important to note that confidential pricing arrangements are likely to be in place and may have a significant impact on the budget impact, as demonstrated in scenario analyses within this HTA.
    - Sensitivity and scenario analysis demonstrated a substantial degree of uncertainty in the estimated budget impact. This was largely due to the

considerable uncertainty relating to the epidemiological inputs, the cost of disease-modifying treatments, and the knowledge gaps related to reimbursement criteria for available disease-modifying treatments.

- Healthcare budgets are limited. In the implementation of any technology, the financial resources for implementation must be found from within the existing health budget or from the wider public sector budget. Consideration must be given to the ethical issues arising from the discontinuance or re-allocation of existing services, within the context of equity and justice for all patients.
- As up to 5% of SMA cases would not be detected by the proposed screening test (that is those with compound heterozygous variants of *SMN1*), it would be important that clinical care pathways ensure that a previous negative screening result does not preclude testing for SMA in such cases presenting symptomatically.
- The benefit-harm balance of screening may differ depending on the *SMN2* copy numbers of the detected SMA case, with patients with lower copy numbers expected to have the most benefit. In particular, the benefit is expected to be more variable in the case of children with four copies of *SMN2*, and is highly uncertain in the case of children with five or more copies given the absence of data in this cohort.
    - Children with higher *SMN2* copy numbers are at higher risk of overtreatment (that is, receiving treatment earlier than would have been required or that might never have been required). An option to mitigate this risk is to adopt a watchful waiting strategy with treatment initiation if there are changes indicative of early disease onset and progression. While this approach likely results in a reduced time to treatment, as compared to absence of screening, there may be harms in terms of psychological distress due to the potential for over-medicalisation of these children and the potential for some irreversible nerve damage prior to treatment initiation.
- Given the disease spectrum and variable potential to benefit, a decision to recommend screening should specify what is meant by a positive screening test and whether the aim is to identify all cases of SMA resulting from a homozygous deletion of *SMN1* or to identify the subset of cases most likely to develop clinically significant disease. There are conflicting ethical implications associated with this decision.
    - Where the aim is to identify a subset of all cases of SMA, the definition of screen positivity could be based on a stated maximum *SMN2* copy number (for example, ≤ 3 copies, ≤ 4 copies). This approach would recognise the correlation between *SMN2* copy number and disease severity, and the uncertainty around the effectiveness (and therefore

cost effectiveness) and or availability of treatment for those with higher *SMN2* copy numbers. As some children with SMA may not benefit from screening, the intention would be to allow early diagnosis and intervention for cases expected to benefit the most from screening. It would also avoid identifying individuals for whom there is substantial uncertainty as to their clinical course and or where adult-onset, mild disease is more likely. This correlation however is imperfect, and the risk of undertreatment and overtreatment cannot be eliminated.

  - If screening were introduced without a threshold, there is a risk of harm for cases identified in terms of psychological distress, over-medicalisation and overtreatment. Introducing a threshold lowers this risk but introduces other risks; cases who were not told about their gene changes could develop symptoms (resulting from irreversible nerve damage) that may have been avoided if they had been monitored and treated earlier as a result of their identification through screening.
  - Where a definition of screen positivity based on *SMN2* copy number is used, this could potentially imply non-disclosure of a genetic diagnosis of SMA to a subset of individuals. People may feel that they have a right to know if they have SMA, even if they are not expected to benefit from early treatment. This must be counterbalanced by the challenges for parents and clinicians of disclosing genetic information that is of uncertain value.

- Due to infrastructural constraints, implementation of screening by the National Newborn Bloodspot Screening Laboratory is unlikely to be feasible until the new children's hospital on the St James's campus is operational. Appropriate resourcing of the National Newborn Bloodspot Screening Programme is essential for the functioning of the programme as a whole.
- In light of the uncertainties identified throughout this HTA, ongoing monitoring of the outcomes of a screening programme for SMA would be important, should a decision be made to recommend screening.

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

- Spinal muscular atrophy (SMA) is a rare, serious genetic condition associated with irreversible motor neuron loss and disease progression. Clinically, the disease presents across a gradient of severity from type 0 (onset in utero, followed by early infant mortality) to type IV (adult-onset).

- Based on historical data, paediatric disease (types I to III) represents 99% of cases identified.
- In Ireland, the median age for diagnosis of type I SMA was six months (range 0 to 7.9 months), type II was 19 months (range 12 to 24 months), and type III was 144 months (range 42 to 192 months).

- Estimates of incidence vary internationally. Data suggest an average of 6.5 cases (95% prediction interval (PI): 2.4 to 13.2) of types I to IV SMA a year in Ireland based on approximately 58,000 births. It is uncertain if screening would be associated with an increase in the number of diagnosed cases of SMA.
- Newborn bloodspot screening for SMA typically targets identification of the homozygous deletion in the survival motor neuron 1 (*SMN1*) gene. This is a reliable and accurate test.
  - This test will, however, not detect cases of SMA that do not involve homozygous *SMN1* deletion (2 to 5% of cases).
- The addition of screening for SMA would enable earlier detection of infants that would otherwise present later with symptoms. Under screening, current clinical subtyping, which is determined by symptomatic presentation and age of onset, would generally no longer apply. Decisions on prognosis and treatment would instead rely on the individual's survival motor neuron 2 (*SMN2*) gene copy number as a biomarker.
- Evidence suggests that earlier treatment with disease-modifying drugs may result in better clinical outcomes by preventing or reducing irreversible motor neuron loss and disease progression.
  - There are limited clinical effectiveness data for all relevant subgroups (for example, presymptomatic populations, and those with higher copy numbers of the *SMN2* gene, indicative of less severe disease). There is also an absence of long-term effectiveness data.
  - The limitations of the effectiveness evidence mean that any estimates of cost effectiveness are highly uncertain.
- While treatments are available for SMA, reimbursement arrangements have not been agreed in the context of screening and would need to be clarified.
- The incremental budget impact associated with the addition of screening for SMA to the National Newborn Bloodspot Screening Programme (that is, the budget impact over and above current expenditure in the absence of

screening), was estimated at approximately €17.7 million (95% confidence interval (CI): €5.1 to €40.5 million) over a five-year time horizon. This was estimated using publicly available drug list prices. The results are subject to considerable uncertainty.

  - Approximately 90% of these costs relate to drug treatment (€16.3 million, 95% CI: €3.8 to €38.9).
  - Total laboratory costs, comprising equipment and consumables associated with screening, were estimated as representing less than 5% of costs (€0.7 million, 95% CI: €0.6 to €0.8).
  - The costs of scheduled healthcare utilisation (€0.1 million, 95% CI: €0.02 to €0.3) and clinical staff (€0.5 million, 95% CI: €0.4 to €0.7) also comprised a small proportion of costs (less than 5%).

- Given the disease spectrum and variable potential to benefit, a decision to recommend screening should specify whether the aim is to identify all cases of SMA resulting from a homozygous deletion of *SMN1* or to identify the subset of cases most likely to develop clinically significant disease. There are conflicting ethical implications associated with this decision. Limiting identification to a subset of cases, on the basis of *SMN2* copy number, would:
  - risk harm in children who could otherwise have been identified through screening, given that *SMN2* copy number is an imperfect biomarker of severity. This would apply specifically to those who may develop clinically significant disease in childhood despite having a higher *SMN2* copy number.
  - potentially imply non-disclosure of a genetic diagnosis of SMA to a subset of individuals. This must be counterbalanced by the challenges for parents and clinicians of disclosing genetic information that is of uncertain value.
- Due to infrastructural constraints, implementation of screening by the National Newborn Bloodspot Screening Laboratory is unlikely to be feasible until the new children's hospital on the St James's campus is operational. Appropriate resourcing of the National Newborn Bloodspot Screening Programme is essential for the functioning of the programme as a whole.

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 spinal muscular atrophy (SMA) to the National Newborn Bloodspot Screening Programme (NNBSP).

Background

In January 2023, 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 SMA to the NNBSP.

Methods

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

- Terms of Reference for the HTA were agreed between HIQA and the NSAC Secretariat.
- 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 NNBSP, the National Newborn Bloodspot Screening Laboratory, clinical and laboratory science experts, patient and public representatives, and international experts.
- The existing and proposed diagnostic and treatment pathways for SMA, and international practice regarding the use of screening for SMA were described.
- The epidemiology and burden of disease of SMA in Ireland and internationally was described.
- A systematic review of the test accuracy and clinical effectiveness of newborn screening for SMA was conducted.
- An overview of the currently available treatments was provided and evidence from clinical trials of disease-modifying treatments was described.

- A systematic review of the cost effectiveness of newborn screening for SMA was conducted.
- The organisational and budgetary implications of introducing newborn screening for SMA in Ireland were described and estimated.
- Wider ethical and societal implications that newborn screening for SMA 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 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 SMA, epidemiology, and burden of disease

SMA is a rare, genetic neuromuscular disorder caused by pathogenic variants in genes that code for the survival motor neuron (SMN) protein. This protein is important for the maintenance of specialised nerve cells (motor neurons) located in the spinal cord and the brainstem. In cases of SMA, insufficient levels of this protein results in progressive and irreversible destruction of the nerve cells in the brain and spinal cord that control movement, leading to muscle wasting and weakness.

Most of the SMN protein is a product of the *survival of motor neuron 1* (*SMN1*) gene. In the majority of individuals with SMA, the condition results from a deletion of a coding region in both copies of the *SMN1* gene. Less frequently, SMA results from a deletion on one of the copies of *SMN1* alongside a smaller change (point mutation) on the other copy. In all of these cases, where the *SMN1* gene becomes non-functional and unable to produce the SMN protein, this is known as '5q-SMA' (so called because the *SMN1* gene is located on the long arm of chromosome 5 (5q)). Almost all cases of SMA are inherited in an autosomal recessive inheritance pattern where each parent is a carrier of the associated genetic pathogenic variant. Where both members of a couple are carriers of SMA, each of their children has a one in four chance of having SMA.

The SMN protein can also be produced from the *survival of motor neuron 2* (*SMN2)* gene. However, only about 10% of the gene-product of *SMN2* is a functional SMN protein. Given the ability of *SMN2* to produce limited amounts of functional SMN protein, this gene can partially compensate for the lack of protein produced due to the deletions in *SMN1*. Higher copy numbers of *SMN2* are associated with lower disease severity and *SMN2* copy number is therefore used as a prognostic biomarker for SMA. However, while a correlation between *SMN2* copy number and clinical severity exists, it is not absolute and discordant cases do present.

In recent years, the availability of disease-modifying therapies has significantly improved the prognosis of individuals with SMA, particularly when initiated early in the disease course. In the absence of disease-modifying treatment, the natural history of SMA is broadly characterised by progressive motor and respiratory muscle wasting and weakness of varying severity. This can result in motor milestones not being reached (for example, sitting, walking), problems with breathing or swallowing for some patients (requiring mechanical ventilation in severe cases), and frequent respiratory infections.

SMA is categorised into five distinct clinical subtypes (type 0 to type IV) based on age of symptom onset and maximum motor function achieved. Symptoms may present at birth (type 0), shortly after birth (type I), during childhood (type II and III) or in adulthood (type IV). Younger age at onset is associated with more severe disease; type 0 which has onset in utero is associated with early infant mortality. Children with type I SMA who do not receive disease-modifying treatment typically do not survive beyond the age of two years. As discussed below, the arrival of these treatments has resulted in substantially improved outcomes for these children. Estimates of the incidence of SMA vary internationally. Data suggest an international incidence of types I to IV SMA of 1 in 8,932, which would equate to an average of 6.5 cases (95% prediction interval (PI): 2.4 to 13.2) a year in Ireland, based on approximately 58,000 births. In Ireland, cases of SMA are currently identified by family history or through clinical presentation. Irish data for diagnosed cases of SMA, for the period 2018 to 2022 suggest an incidence of 1 in 12,211. However, this incidence may be underestimated due to the lack of centralised data collection and the potential for underdiagnosis of milder SMA types. Available national epidemiological data are broadly in line with international estimates, taking small sample sizes and naturally occurring variation in the context of rare diseases into account.

The proportions of SMA cases that are types I to IV were estimated in this HTA through a meta-analysis of published studies. Type I was estimated to comprise 55.3% of cases, followed by type II (23.3%), type III (20.4%) and type IV (1.0%). It is important to note that in the context of newborn bloodspot screening for SMA,

the majority of individuals are asymptomatic at diagnosis. Therefore, introduction of screening effectively removes clinical subtyping; decisions on prognosis and treatment instead rely on genetic phenotype using the patient's *SMN2* gene copy number as a biomarker.

To indicate the likely clinical course for individuals based on *SMN2* copy number, a meta-analysis was undertaken using historical data from patients presenting clinically with symptoms. The majority of these patients were estimated as having up to three copies of *SMN2* (85.0%), and, amongst these, almost all were estimated to present with types I to III SMA (99.8%). An estimated 11.1% (95% confidence interval, CI: 4.3% to 19.9%) had four copies of *SMN2*, of which 94.4% (95% CI: 82.8% to 99.2%) were estimated to present with types I to III, with the remainder presenting with type IV SMA (5.6%, 95% CI: 0.8% to 17.2%). The data suggest that 3.9% (95% CI: 0.0% to 22.8%) had five or more copies of *SMN2*. The percentage of individuals with higher copy numbers is subject to substantial uncertainty due to the very small number of cases with five or more copies that have been diagnosed with SMA in the absence of screening. While the likely SMA type in the absence of treatment is subject to substantial uncertainty, for those with higher *SMN2* copy numbers, the available evidence suggests that these patients would likely have milder disease

In the absence of screening, there may be a delay between symptom onset and diagnosis; this delay could be avoided if a newborn bloodspot screening programme were implemented. The literature suggests that the interval from symptom onset to diagnosis increases as the clinical severity of disease decreases. Type I SMA is associated with the shortest diagnostic delay and type IV with the longest. This likely reflects the challenges in recognising and attributing symptoms, particularly in those with a milder disease course. In the Irish context, data on age of diagnosis were provided by CHI at Temple Street for 25 paediatric cases. Here, the median age at diagnosis for type I SMA was six months (range 0 to 7.9 months), type II was 19 months (range 12 to 24 months), and type III was 144 months (range 42 to 192 months).

Description of technology

This report considers the addition of newborn screening for SMA to the NNBSP in Ireland. Of note, in the event that a decision is made to add SMA to the NNBSP, those with a confirmed high risk of a child with SMA, due to a family history of SMA, would continue to be offered prenatal genetic testing, in line with current practice.

Population-based newborn screening for SMA typically involves testing the infant's genetic material (their DNA) for homozygous deletions in the *SMN1* gene, that is, deletions in both copies of the gene. The DNA is extracted from the dried bloodspot

sample and amplified using quantitative polymerase chain reaction (qPCR)–based techniques to detect the homozygous deletion. This process may be accomplished using commercially available testing kits. Following an initial positive screening test, there is an additional test undertaken, often performed using multiplex ligation-dependent probe amplification (MLPA), to confirm the diagnosis and quantify the number of copies of the *SMN2* gene. The screening test cannot distinguish between SMA types; however, prognostic information can be drawn from the *SMN2* copy number (although, as previously stated, this method is not absolute). Also of note, the proposed screening test only identifies homozygous deletions in the *SMN1* gene and will not identify those with compound heterozygous variants of *SMN1* (up to 5% of SMA cases, where a deletion occurs in one copy of the gene and there is a point mutation in the other).

In terms of current international practice regarding newborn screening for SMA, a review of 34 countries was conducted up to August 2023, including those in the European Economic Area, the United Kingdom, the United States, Canada (provinces), Australia (regions) and New Zealand. Newborn screening for SMA was found to be fully nationally implemented in eight countries, regionally implemented in four countries, under implementation nationally in one country, being piloted in seven countries, and under review in two countries.

In the absence of screening (that is, current practice), cases of SMA are identified by family history or symptomatic presentation. These current diagnostic pathways depend on whether the condition is paediatric-onset or adult-onset. In the paediatric setting, if SMA is suspected, the child is referred for diagnostic testing by a healthcare professional. Diagnostic testing is carried out at the molecular genetics laboratory in the Department of Clinical Genetics at Children's Health Ireland (CHI) Crumlin or, specifically for those seen in the neuromuscular clinic in CHI at Temple Street, by an external provider in Germany. A blood draw is taken and molecular genetic testing is performed to quantitatively analyse *SMN1* and *SMN2.* This is performed using MLPA, qPCR, or next-generation sequencing. The absence of two full *SMN1* copies (suggesting homozygous deletion of the *SMN1* gene) is indicative of a diagnosis of SMA. If only one full copy is present and the clinical presentation is indicative of SMA, the *SMN1* gene is sequenced to check for point mutations.

Once diagnosis is confirmed, the child is seen in the neuromuscular service at CHI at Temple Street, which acts as the national tertiary referral centre for children with SMA. Here, decisions on the treatment are made in conjunction with the family. Siblings of children with SMA are assessed by a clinical specialist for any potential signs or symptoms of SMA. If there is clinical concern, genetic testing is then undertaken. For adults, suspected cases of adult-onset SMA are typically diagnosed

by a local neurologist or through referral to a neurologist with a special interest in neuromuscular conditions.

While paediatric-onset SMA cases will transition to adult services for ongoing treatment and monitoring, currently there are no SMN-dependent drugs reimbursed for the treatment of adult-onset SMA in Ireland. Treatment in adults is supportive in nature and case-specific depending on the clinical needs of the patient.

Clinical effectiveness of screening

In order to describe the clinical effectiveness of newborn screening for SMA, a systematic review of the international literature was undertaken to examine approaches to, and outcomes of, newborn bloodspot screening for SMA. Both comparative studies (which compare clinical outcomes based on the intervention of screening) and non-comparative studies (which report outcomes for population-based newborn bloodspot screening and contribute descriptive information on outcomes such as test performance) of population-based newborn bloodspot screening for SMA were considered eligible.

Thirty-two publications, describing 20 unique studies, were included, consisting of 29 non-comparative publications (17 unique cohorts) and three comparative publications (all unique cohorts). Of the 17 studies providing detail on approaches used, the primary target of screening in all studies was homozygous deletions in *SMN1* using PCR-based methods as the initial test. However, there was variation in the use of second tier tests, test targets, confirmatory testing methods, and laboratory techniques. Eight studies included a second tier test to confirm *SMN1* deletions and or quantify *SMN2* copy number. In two studies, the number of *SMN2* copies was used to establish a cut-off for screen positives (meaning that those identified as having more than the specified *SMN2* copy numbers were not reported as having SMA). In both of these studies, the use of *SMN2* cut-offs for test positivity (four or more copies or five or more copies) was related to the uncertainty associated with the prognostic value of higher copy numbers.

Following a positive result on a screening test, confirmatory testing is undertaken to establish a diagnosis. In the studies examined, as a percentage of the total population screened, referrals for confirmatory testing ranged from <0.01% to 0.14%, with the midpoint being 0.01% (that is, 1 in 10,000). The positive predictive value (PPV) of a test means the probability that when a test result is positive, the person truly has the condition. Across studies, the PPV ranged from 16.67% to 100%, with the midpoint being 100% and 13 studies reporting a PPV at or above 90%. As a percentage of the total population screened, this reflected a false positivity rate for the screening test (that is, the number of those without the condition that are incorrectly classified as positive by the test) of less than 0.01% (<

1 in 10,000) in all but one study (0.13%). Based on pooled data across the 16 studies which reported false positivity rates, the ratio of SMA cases to false positive cases was 6:1. In included studies, factors noted to influence test accuracy included contamination, and human or system errors.

Collectively, over 3.2 million infants were screened, with 240 cases of SMA identified through screening. The majority of these cases had two (n = 118, 49%) or three (n = 71, 30%) *SMN2* copies. Symptom status was reported for 212 cases with 68 (32%) noted to be symptomatic at some point within the screening pathway up to and including treatment initiation. The majority of those that were symptomatic within the screening pathway had two *SMN2* copies (n = 51, 75%). The reported incidence rate of SMA associated with homozygous deletions ranged from 1 in 6,059 to 1 in 19,000 (midpoint 1 in 13,500) across the studies. Considering the total number of SMA cases detected and the total number of infants screened in these studies, a collective incidence of 1 in 14,574 is estimated. Given the relatively recent introduction of newborn screening for SMA, it is difficult to assess the impact of screening on SMA incidence, that is, whether it results in an increase in the total number of cases that are identified.

Limited data on the impact of newborn screening on morbidity were identified from three comparative studies, with all three presenting a potential positive impact. One study explicitly compared outcomes in a screened cohort with an unscreened cohort, with evidence to suggest significantly improved functional outcomes with screening. While providing promising results of the effect of newborn screening on clinical outcomes, these studies included small sample sizes, were restricted to a maximum of two years of follow-up data, and are inherently linked to the long-term effectiveness data of disease-modifying interventions, which is also limited at present.

With respect to consideration of the potential harms of screening, it is noteworthy that it may be possible to perform confirmatory testing on the original bloodspot sample taken for the purpose of newborn screening. If this is the case, this would mean that there would be no need to contact the family for a separate blood draw, thereby minimising the impact of a false positive screening result on them. The need for a separate blood draw would however depend on the outcomes of the verification process (that is, the phase in which the testing method is established, which occurs prior to implementing screening in the population).

Overview of treatment

There is currently no known cure for SMA; historically SMA was managed symptomatically through supportive therapies. However, treatments are now available which serve to increase production of the SMN protein and thereby aim to

alter disease processes. The first drug was licensed by the European Medicines Agency (EMA) in 2017. As of September 2023, there are three SMN-dependent drugs licensed by the European Medicines Agency: nusinersen, onasemnogene abeparvovec (OA), and risdiplam.

The drugs differ in their mechanisms of action, treatment duration, and administration schedules. Both nusinersen and risdiplam act to enhance the production of SMN protein from the *SMN2* gene, and both may be administered for an indefinite duration provided the patient continues to benefit from treatment. Nusinersen is administered via intrathecal injection initially every 14 days, with the interval increasing over time to administration once every four months. Risdiplam is administered via oral solution daily. OA is a gene therapy which acts to replace the missing or non-functional *SMN1* gene. This treatment is administered as a one-off therapy via intravenous infusion.

These drugs are associated with very high drug acquisition costs. Annual costs to the HSE based on the list price were estimated as approximately €255,000 per patient for each of nusinersen and risdiplam and €2.2 million per patient for OA when administered as a one-off treatment. The actual costs to the HSE are anticipated to be lower, but this cannot be confirmed due to the confidential nature of the agreements.

Access to treatment is available in the publicly funded healthcare system in Ireland for children with symptomatic SMA subject to managed access protocols. However, cases of type 0 SMA are managed with supportive and palliative care, including family counselling. With regard to treatment availability for patients who are not yet symptomatic (as would be the case for most patients identified through screening), at least one treatment is currently reimbursed through the publicly funded healthcare system for patients who have up to three *SMN2* copies. However, it is noted that current reimbursement criteria were agreed in the absence of a screening programme and will likely also change over time in line with emergence of new evidence. Reimbursement arrangements in the context of screening would need to be clarified.

Published interim efficacy data for presymptomatic treatment initiation were identified from three ongoing trials. One trial each was identified for nusinersen (n = 25), OA (n = 29), and risdiplam (n = 6) with follow-up ranging from 12 months to a median of 2.9 years. The studies were all single-arm and the reported findings are limited to individuals with two or three copies of *SMN2*. Across the three trials, all patients were alive at follow-up, with no patient requiring permanent mechanical ventilation. Functional outcome data indicated that the majority of children achieved their motor milestones within the normal development range.

In terms of efficacy data for symptomatic treatment initiation, five pivotal trials that informed the EMA authorisation of the three drugs were identified. Overall, these were limited in terms of study size and follow-up duration. Results published to date demonstrate motor and developmental improvements across studies. Data from the studies of nusinersen and OA in patients with type I SMA indicate improved event-free survival (that is, absence of death or permanent ventilation) compared with a control group and natural history cohort, respectively.

No trials were identified that directly compared presymptomatic initiation of treatment to treatment once a patient with SMA has become symptomatic. Evidence from a subgroup analyses of trials in the symptomatic setting suggests that early treatment with nusinersen may be associated with greater improvement compared with later treatment. Unadjusted comparisons of outcomes observed in clinical trials, for patients expected to develop type I SMA and who were treated with nusinersen or OA, suggest that presymptomatic treatment may lead to improved outcomes compared with symptomatic initiation. However, such comparisons are heavily prone to bias.

Overall, while treatment-related adverse events were reported, few serious safety concerns were identified in the clinical trials examined. Serious liver failure and acute liver failure (including two fatal cases) have been reported with OA post authorisation.

In summary, based on limited data, there is evidence that in symptomatic individuals these drugs lead to improved outcomes relative to the natural history of the disease. Fewer data are available for presymptomatic patients, with some evidence of improvement for those with two or three copies of *SMN2*. The evidence (primarily in type I disease) also suggests that earlier treatment may be more beneficial than later treatment. Follow-up data are limited and therefore there is substantial uncertainty regarding the long-term effectiveness of these treatments.

Systematic review of the cost effectiveness of screening

A systematic review was undertaken to synthesise and critically appraise the international evidence on the cost effectiveness of newborn screening for SMA (including subsequent treatment) compared with clinical presentation. Five studies, including four cost-utility analyses (CUA) and one cost-effectiveness analysis (CEA), met the inclusion criteria.

Changes in the treatment landscape over time and variation in methodological approaches contributed to an extremely wide range of results in terms of the cost per quality-adjusted life year (QALY) gained. Compared with clinical presentation, newborn bloodspot screening for SMA was considered cost saving in two CUAs; in

these studies, a substantial proportion of patients identified by screening were modelled as being treated with OA. In contrast, in one CUA, newborn bloodspot screening with nusinersen treatment, relative to clinical presentation, was not found to be cost effective (adjusted incremental cost-effectiveness ratio (ICER) €231,004 per QALY), given a willingness-to-pay threshold of €45,000 per QALY gained. Finally, in one CUA, the ICER varied between not cost effective (adjusted ICER €307,746 per QALY gained) and cost saving, depending on the treatment strategy. All of the models were highly sensitive to the cost of the treatment strategy, and sensitive to a lesser extent to resource use, utility values and incidence of SMA.

Due to limitations in the evidence base, including the absence of long-term clinical effectiveness data, limited comparative data for screened versus non-screened populations, and a lack of evidence for those with higher copy numbers, as well as concerns regarding the modelled assumptions, conclusions regarding the cost effectiveness of screening could not be made. Given these limitations in the clinical evidence base, de novo modelling to inform cost effectiveness of screening in the Irish setting was not undertaken.

Organisational aspects and budget impact analysis

In terms of changes to practice within the current NNBSP, beyond the common changes with the addition of any condition to the programme, it is not anticipated that the addition of screening for SMA would result in any specific change to overall practice within the NNBSP. The NNBSP highlighted that, with the exception of the laboratory staffing changes described below, the NNBSP itself would be unlikely to require additional staff if screening for SMA were implemented, provided the current requirements submitted as per the HSE National Service Plan for 2024 are fulfilled.

Considering processes regarding informed consent, as with the addition of any new condition to the NNBSP, there would be a need to update written material and processes associated with informed consent for testing.

In 2023, it was agreed that the NNBSP should be expanded to include screening for severe combined immunodeficiency (SCID). In terms of laboratory considerations, screening for SMA involves the same PCR-based technology as screening for SCID and there are commercially available multiplex assays which allow for concurrent screening for these two conditions. Should screening for SMA be recommended, this would potentially result in operational efficiencies in terms of the equipment requirements, physical space requirements, training needs of staff, and verification and screening processes, as compared to a scenario where SMA were to be introduced in the absence of screening for SCID. It is not anticipated that verification of the testing method could begin prior to the laboratory at the new children's hospital being operational. However, verification and implementation of the testing

methods for SMA and SCID screening could take place concurrently. Therefore, no additional laboratory staff would be required under the assumption that staff requirements submitted as part of the HSE National Service Plan to implement TREC-based screening for SCID are met. A decision would be required on the location of second-tier testing using MLPA methodology; this would require consideration of factors such as demand for testing, and the expertise and equipment required.

In terms of management pathways, in the context of newborn screening for SMA, decision-making regarding treatment would likely be made on the basis of *SMN2* copy number and, for the majority of cases, in the absence of a known SMA type. The introduction of screening for SMA would also likely result in some patients following an alternative treatment pathway than they would have followed if they had presented symptomatically at a later point. This would have resource and budget implications for the HSE. Additionally, a small number of those identified as having SMA may not meet the criteria for, or consent to, immediate treatment. Inclusion of a watchful waiting strategy within the management pathway would need to be considered.

A budget impact analysis was undertaken to estimate the incremental budget impact associated with the addition of screening for SMA to the NNBSP relative to identification based on clinical suspicion or family history. For patients with a diagnosis of SMA, the treatment pathway was determined according to disease type (meaning SMA types I to IV) in the current care arm, and *SMN2* copy number in the screening arm.

The incremental budget impact associated with the addition of screening for SMA to the NNBSP (that is, the budget impact over and above current expenditure in the absence of screening), was estimated at approximately €17.7 million (95% CI: €5.1 to €40.5 million) over a five-year time horizon. Total laboratory costs, comprising equipment and consumables associated with screening, were estimated as representing less than 5% of costs (€0.7 million, 95% CI: €0.6 to €0.8). The costs of scheduled healthcare utilisation (€0.1 million, 95% CI: €0.02 to €0.3) and clinical staff (€0.5 million, 95% CI: €0.4 to €0.7) also comprised a small proportion of the total incremental budget impact (less than 5%). The majority of expenditure over this period (greater than 90%) related to drug costs (€16.3 million, 95% CI: €3.8 to €38.9 million). This was primarily accounted for by changes to the treatments that would be received by individuals under screening. Specifically, more individuals were modelled as receiving one-off treatment with onasemnogene abeparvovec than would receive it under current care. Without screening, these cases would be treated later, for an indefinite duration, with nusinersen or risdiplam. As onasemnogene abeparvovec is associated with a very high upfront cost, its contribution to the

overall budget impact is particularly observed over shorter time horizons (such as the five years modelled). However, use of a longer time horizon would be subject to even greater uncertainty given the evolving treatment landscape. Of note, drug costs were calculated based on the publicly known list price. Confidential pricing arrangements are likely to be in place and may have a significant impact on the incremental budget impact, as demonstrated in scenario analyses within this HTA.

Given a high level of uncertainty is inherent to research related to rare diseases, extensive sensitivity and scenario analyses were undertaken. These demonstrated a substantial degree of uncertainty around the estimated incremental budget impact, largely due to the considerable uncertainty relating to the epidemiological inputs, the cost of disease-modifying treatments (in particular the potential for confidential pricing agreements), and the current knowledge gaps related to reimbursement criteria for available disease-modifying treatments.

Ethical and social considerations

The benefit - harm balance of screening may differ depending on the *SMN2* copy number of the detected SMA case; individuals with lower copy numbers would be expected to have the most benefit given their higher likelihood of severe disease. Were current treatment access arrangements in Ireland to hold in the context of screening being in place, those with fewer than four copies of *SMN2* (the majority of patients with SMA) would likely have earlier access to treatment, leading to improved clinical outcomes. However, as *SMN2* copy number is not fully predictive of SMA severity, some of these individuals are at risk of overtreatment (receiving treatment earlier than would have been required or that might never have been required) or would receive a different treatment to that which they would have received in the absence of screening. In particular, the benefit is expected to be more variable in the case of children with four copies of *SMN2*, and is highly uncertain in the case of children with five or more copies given the absence of data in this cohort.

Children with higher *SMN2* copy numbers are at higher risk of overtreatment (that is, receiving treatment earlier than would have been required or that might never have been required). An option to mitigate this risk is to adopt a watchful waiting strategy with treatment initiation if there are changes indicative of early disease onset and progression. While watchful waiting likely results in a reduced time to treatment than would occur in the absence of screening, there may be harms in terms of psychological distress due to the potential for medicalisation of these children following identification through screening. Also, adoption of a watchful waiting approach would mean there is greater potential for some irreversible nerve damage prior to treatment initiation compared to a scenario where treatment is initiated soon after diagnosis.

With regards to autonomy, screening for SMA involves a particularly vulnerable population (newborns) with consent for screening and decision-making for care deferred to parents. The informed consent process needs to be clear that SMA caused by compound heterozygous variants of *SMN1* (up to 5% of SMA cases) would not be detected by the screening test. It would be important that clinical care pathways ensure that testing for SMA is considered in children who present symptomatically even if they had a 'not suspected' (negative) screening test. Additionally, it is important to note that screening of newborns for SMA may result in subsequent identification of other family members as either being affected with SMA or as carriers.

In this way, screening for SMA may have implications for the families of those identified as part of the screening programme in terms of autonomy. Where a case of SMA is identified, some members of the family of the newborn may also be offered cascade testing to aid in the identification of sibling cases or carriers. For some, this might be beneficial in that it may facilitate earlier access to treatment or inform future family planning. However, individuals may experience psychological distress associated with this information, or feel that they are being labelled unnecessarily.

Given the disease spectrum and variable potential to benefit, a decision to recommend screening should specify what is meant by a positive screening test and whether the aim of screening should be to identify all cases of SMA resulting from a homozygous deletion of *SMN1* or just to identify the subset of cases most likely to develop clinically significant disease. If a definition of screen positivity based on *SMN2* copy number is used, this could potentially imply non-disclosure of a genetic diagnosis of SMA to a subset of individuals, which may have important ethical implications. People may feel that they have a right to know if they have SMA, even if they are not expected to benefit from early treatment. These would need to be balanced against the ethical implications of classifying a person as a 'case' when it is uncertain if or when they might present with clinical symptoms.

From the justice and equity perspective, healthcare budgets are finite. In the implementation of any technology, the financial resources for implementation must be found from within the existing health budget or from the wider public sector budget. Consideration must be given to the ethical issues arising from the discontinuance or re-allocation of existing services, within the context of equity and justice for all patients. This is particularly relevant when considering the cost of the disease-modifying treatments for SMA, and the uncertainties that exist in the estimates of the cost effectiveness and budget impact of adding screening for SMA to the NNBSP.

Conclusion

SMA is a rare genetic neuromuscular disorder characterised by significant morbidity and mortality. The condition results in irreversible degeneration of motor neurons in the spinal cord, resulting in progressive muscle wasting and weakness, and occurs across a gradient of severity. The proposed screening method accurately identifies homozygous deletions of the *SMN1* gene which are associated with at least 95% of cases of SMA. It will not detect cases of SMA that do not involve homozygous *SMN1* gene deletion (2-5% cases).

Based on limited data, there is evidence to suggest that screening, compared with no screening, is associated with clinical benefits, due to earlier identification and access to disease-modifying treatment, for those who would otherwise develop type I to type III disease. However, due to the absence of complete correlation between *SMN2* copy number and SMA type, it is not possible to predict with certainty which patients will develop severe disease. As such, the benefit – harm balance in the context of screening varies.

Given the disease spectrum and variable potential to benefit, a decision to recommend screening should specify whether the aim is to identify all cases of SMA resulting from a homozygous deletion of *SMN1* or to identify the subset of cases most likely to develop clinically significant disease. A definition of screen positivity could be devised based on *SMN2* copy number such that only those with SMA who have a copy number within a certain range are disclosed as being screen positive. There are potential ethical issues that would arise from limiting identification to a subset of cases on the basis of *SMN2* copy number. These include a risk of harm in children who could otherwise have been identified through screening, given that *SMN2* copy number is an imperfect biomarker of severity. However, this risk would need to be balanced against the ethical implications of identifying babies as having a condition in the absence of a clear correlation between genotype and phenotype.

The potential benefits of a screening programme, comprising end-to-end care, need to be considered in light of key uncertainties including the epidemiology of SMA types in Ireland, a rapidly evolving treatment landscape, a lack of long-term effectiveness data and uncertainty regarding reimbursement criteria in the context of screening. These knowledge gaps combine to produce significant uncertainty regarding the cost effectiveness and affordability of screening. In light of these uncertainties, ongoing monitoring of the outcomes of a screening programme for SMA would be important, should a decision be made to recommend screening.

Plain language summary

Screening can help people with rare and serious conditions to be identified and treated sooner. Earlier treatment means they might live longer or have a better quality of life. The National Newborn Bloodspot Screening Programme carries out the heel prick test. This involves a small sample of blood being taken from a baby's heel in the first 72 hours after they are born. The sample is then sent to a laboratory and tested for several conditions. The programme currently screens for nine conditions. In January 2023, the Minister for Health approved the addition of a tenth condition to the programme.

Spinal muscular atrophy (SMA) is a rare, serious condition. Through screening, SMA can be identified in newborns. The National Screening Advisory Committee requested that the Health Information and Quality Authority (HIQA) examine the available information on screening of newborns for SMA. This work was done to inform a decision on whether SMA should be added to the existing National Newborn Bloodspot Screening Programme.

SMA is caused by changes in a gene within a person's DNA. SMA causes permanent damage to the motor nerves. This damage causes muscles to become weaker over time. As these muscles become weaker, it can make it challenging for a person to do activities like walking, talking, and even breathing.

There are five different types of SMA. The type of SMA a person has is based on the age at which they start to show symptoms and the movement milestones they reach, for example, sitting or walking. Without treatment, some SMA types can cause early death, or result in serious disabilities in childhood such as problems with walking or breathing. Other SMA types can be associated with developing symptoms later in childhood or as an adult, and in having less severe symptoms. It is more common for SMA to be severe than to be mild. In Ireland, on average, around seven babies a year are expected to be born with SMA, though this number will likely differ from year to year.

Until a few years ago, children with SMA were given physical therapy, nutritional support, and breathing support to help manage their symptoms. No treatments were available that could stop the disease from progressing. Since 2017, new drug treatments specifically for SMA have become available. There are now three drugs licensed in Europe for SMA. As the drug treatments are quite new and as SMA is a rare disease, evidence of how well they work is limited. Some studies suggest that they can help to maintain muscle function in babies and children with SMA. The drugs cannot reverse any existing damage, so these treatments likely work better the sooner they are given. This would be an advantage of screening – if babies with

SMA are identified and treated sooner, it could help stop further muscle damage or even stop the damage occurring in the first place.

SMA is a genetic condition. This means it can be passed from parents to children. Parents can pass along SMA without having SMA themselves. To screen for SMA in infants, the blood sample taken from the baby's heel is checked for the gene changes that happen in SMA. This screening test is very accurate. If the screening test suggests that the baby has SMA, scientists can do another test to confirm the result and get an idea of how serious the disease might be. This second test is important as the information it provides may be used to decide what treatment, if any, should be offered to the child. However, the screening test only works for some gene problems. Up to one in every 20 babies with SMA have a different gene problem and cannot be identified by this screening test. These children would not benefit from the introduction of screening for SMA.

While the treatments for SMA may help children with SMA, they are very expensive. Depending on the treatment used, it could cost over €300,000 a year for each patient (for treatments given regularly) or €2.2 million for each patient for a one-off treatment. Not many studies have been carried out to see whether or not screening for SMA would be a good use of the healthcare budget. The studies that have been carried out do not answer the question fully and did not all agree on the answer. As a result, it is unclear if screening for SMA gives good results for the amount of money spent.

Including the cost of treatment, it is estimated that screening for SMA would cost about €18 million over the first five years after it is introduced. This number is very uncertain. The amount could be higher or lower, as the full information on prices for testing and treatments is not available. Also, with screening, the upfront costs of treatment would be very high. This is because more patients would receive a one-off treatment.

Some children with SMA may not benefit from screening. Some children identified as having SMA may not require treatment until they are adults. It is possible that some children might be treated who would have never needed treatment. Sometimes a child may be identified through screening as having SMA but may never even develop any symptoms. A diagnosis of SMA will result in upset for patients and their families. Patients and their families would need to have access to support and education to help them cope with the diagnosis. As SMA is a genetic condition they would also need to think about testing their other family members for the gene problem. Parents of a child with SMA might also want information to support their future family planning.

With screening, decision-makers would have to say what they mean by a positive screening test. It could be everyone with a change in the gene or only those that are most likely to develop symptoms of the disease earlier in life or who are more likely to have serious symptoms. If a positive screen were based on those most likely to develop serious symptoms this would impact on a small number of cases and raise the following concerns. People may feel that they have a right to know if they have SMA, even if they are not expected to benefit from early treatment. However, having this information means they and their families will need to live with this diagnosis, and think about what it means for their family and any future children they may have. It is not possible to be certain about which patients will develop severe disease. If some people are not told about their gene changes, there is a risk that they could develop symptoms that could have been avoided. Another option is for a specialist team to monitor children who are at lower risk of severe disease, and to start treatment if symptoms develop. Although these concerns only apply to a small number of cases, decision-makers have to carefully consider the impact of these choices.

Overall, SMA is a very rare and serious condition. Screening for SMA is very accurate and can identify most babies with SMA before they start to show symptoms. It is not known if all people with the gene change will eventually develop symptoms of SMA. Treatments for SMA may work better if given earlier. These treatments are very expensive, and not a lot is known about how well they work in the long term. Screening is expected to benefit most children with SMA, but may not benefit all. It is important that all of these points are considered before a decision is made on whether or not SMA screening is introduced.

List of abbreviations used in this report

AAV9	adeno-associated virus 9
BIA	budget impact analysis
BSID-III	Bayley Scales of Infant and Toddler Development Third Edition
CEA	cost-effectiveness analysis
CHEC	Consensus on Health Economics Criteria
CHI	Children's Health Ireland
CHMP	Committee for Medicinal Products for Human Use
CHOP-INTEND	Children's Hospital Of Philadelphia Infant Test Of Neuromuscular Disorders
CI	confidence interval
CMAP	compound muscle action potential
CNS	central nervous system
CPI	consumer price index
CPU	Corporate Pharmaceutical Unit
Ct	cycle threshold
CUA	cost-utility analysis
DBS	dried bloodspot
ddPCR	digital droplet polymerase chain reaction
DNA	deoxyribonucleic acid
DoH	Department of Health
DRG	Diagnosis related Group
EAG	expert advisory group
EQ-5D-3L	EuroQol 5-dimensions with 3-levels
EMA	European Medicines Agency
EMG	Electromyography
EUnetHTA	European Network for Health Technology Assessment
FDA	US Food and Drug Administration
GLMM	generalised linear mixed methods
GMFM	Gross Motor Function Measure
GP	General Practitioner
HFMSE	Hammersmith Functional Motor Scale Extended
HINE	Hammersmith Infant Neurological Examination
HIQA	Health Information and Quality Authority
HR	hazard ratio
HR-QoL	health related quality of life

HSE	Health Service Executive
HTA	health technology assessment
ICER	incremental cost-effectiveness ratio
ICT	information and communication technology
IQR	interquartile range
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
IVD	*in vitro* diagnostic medical devices
LYG	life year gained
MAP	managed access protocol
MCID	minimal clinically important differences
MDT	multidisciplinary team
MFM	Motor Function Measure
MLPA	multiplex ligation-dependent probe amplification
MMP	HSE Medicines Management Programme
NBS	newborn bloodspot screening
NMB	monetary benefit
NCPE	National Centre for Pharmacoeconomics
NNBSL	National Newborn Bloodspot Screening Laboratory
NNBSP	National Newborn Bloodspot Screening Programme
NSAC	National Screening Advisory Committee
OA	onasemnogene abeparvovec
PCR	polymerase chain reaction
PI	prediction interval
PICOS	Population, Intervention, Comparator, Outcomes and Study design
PNCR	Paediatric Neuromuscular Clinical Research
PPP	purchasing power parity
PPV	positive predictive value
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QALY	quality-adjusted life year
qPCR	quantitative polymerase chain reaction
RCT	randomised controlled trial
RULM	Revised Upper Limb Module
SCID	severe combined immunodeficiency
SD	standard deviation
SMA	spinal muscular atrophy

SMN	survival motor neuron (protein)
SMN1	survival motor neuron 1 (gene)
SMN2	survival motor neuron 2 (gene)
SmPCs	Summary of Product Characteristics
TREC	T-cell receptor excision circles
VAS	visual analogue scale
VAT	value added tax
WHO	World Health Organization
WTE	whole time equivalent
WTP	willingness to pay
XLA	X-linked agammaglobulinemia
6MWT	6 minute walk test

1 Introduction

1.1 Background to the request

Spinal muscular atrophy (SMA) is a rare, genetic neuromuscular disorder.[1, 2] There are five subtypes of SMA, distinguished by clinical severity, with more severe forms typically presenting in infancy and early childhood, and milder forms presenting in later life.[3-5] While the severity of SMA varies, it is characterised by irreversible degeneration of motor neurons in the spinal cord resulting in progressive muscle wasting and weakness.[4, 5] SMA was historically associated with supportive care only. However, in recent years a number of disease-modifying treatments have been approved for use in the European Union.[3-6]

Given the pathophysiology associated with SMA, there is clinical rationale and emerging evidence to suggest that earlier identification and initiation of treatment may improve overall outcomes.[4-6] Newborn bloodspot screening for SMA is possible and has been implemented in a number of countries internationally, with that number anticipated to increase over the coming years given the recent availability of treatments.[7]

There are a number of considerations that need to be taken into account within decision-making for screening programmes. In October 2020, the National Screening Advisory Committee (NSAC) produced a modified list of 20 criteria for appraising the viability, effectiveness and appropriateness of a screening programme.[8] These criteria are presented in Appendix Chapter 1, Table A1.1 in a categorised format (that is, under the headings of 'condition', 'screening method', 'intervention', 'screening programme', and 'implementation'). A health technology assessment (HTA) may be used to systematically synthesise information to inform these criteria.

In response to the Department of Health's 2021 Annual Call, a proposal was submitted to NSAC to consider the introduction of screening for spinal muscular atrophy (SMA) as part of the National Newborn Bloodspot Screening Programme (NNBSP).[9] This proposal was subsequently prioritised by NSAC and a request was submitted to the Health Information and Quality Authority (HIQA) to undertake a HTA on this topic.

1.2 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. The terms of reference for this HTA, as agreed with the NSAC Secretariat in the Department of Health, were to:

- Describe the existing and proposed diagnostic and treatment pathway for spinal muscular atrophy (SMA) in Ireland.
- Conduct a review on the international practice of the use of newborn bloodspot screening for SMA.
- Describe the epidemiology and burden of disease of SMA.
- Perform a review of the test accuracy of newborn bloodspot screening for SMA.
- Describe the clinical effectiveness of screening for SMA, and of the available disease-modifying treatment options in Ireland.
- Assess the cost effectiveness, budget impact, and resource implications of introducing newborn bloodspot screening for SMA.
- Consider any wider organisational, ethical or societal implications that newborn bloodspot screening for SMA may have for patients, families, the general public or the healthcare system in Ireland.
- Produce a report summarising the above pieces of work.
- Convene meetings of the HIQA Expert Advisory Group (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.

1.3 Overall approach

A multidisciplinary EAG was convened by HIQA comprising representation from relevant stakeholders including the Department of Health, the Health Service Executive (HSE), the NNBSP, National Newborn Bloodspot Screening Laboratory, clinicians with specialist expertise in paediatric neurology, adult neurology, public health, and clinical genetics, two patient and public representatives (SMA Ireland and Cuidiú) and international experts. The role of the EAG was 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 and the draft chapters of the description of technology, clinical effectiveness, overview of treatments, and the systematic review of economic literature were discussed. Consideration of the epidemiology, budget impact, organisational implications, and ethical and social considerations were discussed at the 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

- Newborn bloodspot screening is offered to all newborns in Ireland within the first 72 to 120 hours of life through the National Newborn Bloodspot Screening Programme (NNBSP). Screening is performed through the collection of a dried bloodspot sample, with samples tested at the National Newborn Bloodspot Screening Laboratory (the 'heel-prick test').
    - The programme currently screens for nine conditions. Addition of severe combined immunodeficiency (SCID) to the programme was approved by the Minister for Health in January 2023 and is undergoing implementation.
- This assessment considers the addition of 5q spinal muscular atrophy, hereafter referred to as spinal muscular atrophy (SMA), to the NNBSP in Ireland.
- SMA is a rare, genetic, neuromuscular disorder characterised by muscle weakness and atrophy. The disease is categorised into five distinct subtypes across a continuous gradient of age and severity from prenatal onset in type 0 to adult onset in type IV.
    - Genetically, SMA is marked by deletions in the survival motor neuron 1 (*SMN1*) gene and is modified by the copy number of a second gene known as survival motor neuron 2 (*SMN2*). Typically, the more copies of *SMN2* an individual has, the less severe the disease tends to be.
- In the absence of newborn bloodspot screening, detection of SMA relies on:
    - screening on the basis of family history or known carrier status of parents (prenatal or cascade testing),
    - clinical presentation through the recognition of symptoms synonymous with the disease.
- Newborn bloodspot screening for SMA is possible through the detection of homozygous deletions (that is, a deletion is present on both versions of the gene) of *SMN1* using polymerase chain reaction (PCR)-based methods on dried bloodspot samples. Positive screens typically undergo testing to confirm *SMN1* deletions and to quantify *SMN2* copy number in order to inform treatment planning.

  - As of August 2023, at least two commercial multiplex assays are available, both of which have capability for dual testing of SCID and SMA.
  - As the screening test targets homozygous deletions, it will not detect cases of SMA caused by other variants (estimated as up to 5% of all SMA cases).
  - The PCR-based screening test cannot distinguish between SMA subtypes and as such will detect all SMA cases with homozygous deletions. This includes those who would not otherwise present until later childhood or into adulthood.
  - It may be possible for the confirmatory test to be performed on the original bloodspot sample, thereby removing the need for an additional blood draw. A decision on the most appropriate sample would depend on the outcomes of the verification process undertaken by the laboratory (that is, the phase in which the testing method is established, which occurs prior to implementing screening in the population).

- International recommendations for the diagnosis of SMA exist and there is a defined diagnostic pathway in Ireland. For paediatric cases, this is centralised to Children's Health Ireland (CHI) at Temple Street, while adult-onset cases are referred to neurologists locally.
- Treatment options for SMA include supportive and disease-modifying treatments. Under the current standard of care in Ireland (that is, symptomatic presentation), disease-modifying treatments are reimbursed (that is, are available through the publicly funded healthcare system) for patients with SMA types I, II, and III.
  - Currently no disease-modifying treatments are available in Ireland for patients with type 0 or type IV SMA.
- In the context of newborn bloodspot screening, indications for disease-modifying treatments rely on the prognostic value of the quantification of *SMN2* copy number. International treatment pathways have typically included a 'watchful waiting' strategy in asymptomatic individuals with higher *SMN2* copy numbers.
  - A possible treatment pathway has been outlined for the Irish context for the purposes of this HTA. Under this pathway, prenatal onset type 0 cases would continue to be treated with supportive care, while symptomatic and asymptomatic cases with three or fewer copies of

SMN2 would likely receive immediate treatment. Asymptomatic cases with four or more copies of *SMN2* would be monitored under a 'watchful waiting' strategy with treatment initiated at symptom onset.

- Should a decision be made to implement SMA screening, a working group of stakeholders, including clinical specialists, would be established in order to outline the associated pathways.

- A review of international screening practice was undertaken to understand the status of screening for SMA internationally. This review examined 34 countries considered 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.
  - International practice in terms of newborn bloodspot screening for SMA is undergoing substantial change. While only fully implemented at a national level in eight countries, screening has been implemented at a regional level in an additional four countries, is under implementation in one country, is being piloted in seven countries, and is under review in two further countries.
  - Of the countries considered, almost all base their definition of screen positivity solely on homozygous deletion of exon 7. In two countries, the definition also takes account of the *SMN2* copy number, with those with more than three or more than four *SMN2* copy numbers not considered to be screen positive.

The purpose of this chapter is to describe key elements of the technology under consideration. The current National Newborn Bloodspot Screening Programme (NNBSP) in Ireland is briefly described followed by the diagnostic and treatment pathways for spinal muscular atrophy (SMA). An overview of newborn bloodspot screening for SMA is presented alongside the status of such screening internationally.

2.1 National Newborn Bloodspot Screening Programme

The organisation, governance, and processes of the NNBSP have been previously described in a HTA published by HIQA in 2023.[10] Briefly, the NNBSP is offered to all newborns in the first 72 to 120 hours of life using a dried bloodspot (DBS) sample taken from the newborn's heel (the 'heel prick test') and tested at the National Newborn Bloodspot Screening Laboratory (NNBSL). The programme currently screens for nine rare but serious conditions; these are:

- 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.

Following a HIQA HTA, severe combined immunodeficiency (SCID) was given a positive recommendation by the National Screening Advisory Committee (NSAC), received approval for addition to the programme from the Minister for Health in January 2023, and is undergoing implementation.[11]

2.2 Spinal muscular atrophy

The condition of relevance to this assessment is SMA. This section provides a brief background to the condition, followed by a description of the current associated diagnostic and treatment pathways for SMA. The aetiology, genotypes (genetic makeup) and phenotypes (observable traits) of SMA are discussed in further detail in

chapter 3: epidemiology, with this chapter also providing a more detailed description of the clinical presentation and burden of disease.

2.2.1 Aetiology

SMA is a rare, genetic neuromuscular disorder caused by pathogenic (disease-causing) variants in genes that code for the survival motor neuron (SMN) protein.[12] The SMN protein is found throughout the body, with highest levels in the spinal cord. This protein is important for the maintenance of specialised nerve cells (motor neurons) located in the spinal cord and the brainstem. In cases of SMA, an absence of a sufficient level of this protein results in progressive and irreversible destruction of the nerve cells in the brain and spinal cord that control movement, leading to muscle wasting and weakness.[3, 13, 14] Most of the SMN protein is a product of the survival of motor neuron 1 (*SMN1*) gene on the long arm of chromosome 5 (5q). The survival of motor neuron 2 (*SMN2)* gene also encodes the SMN protein; however, only about 10% of the gene-product is a full length SMN protein.[15] The number of *SMN2* copies acts as a modifier of functional SMN production such that greater numbers of *SMN2* copies (in the absence of *SMN1*) affords greater functionality.[16-18]

Most cases (approximately 95%) of SMA are caused by a homozygous (that is, involving both versions of the gene, known as alleles) deletion of exon 7 of the *SMN1* gene. Less frequently (in up to 5% of cases), SMA results from a deletion of exon 7 on one of the copies of *SMN1* alongside a smaller, more specific pathogenic variation (point mutation) on the other copy of *SMN1* (henceforth referred to as compound heterozygous variants).[19] In all of these cases, where the *SMN1* gene becomes non-functional and unable to produce the SMN protein, this is known as 5q-SMA. In rare cases, pathogenic variants in other genes can also cause SMA; such cases of SMA are known as 'non-5q SMA'.[20, 21] This group represents clinically overlapping, yet separate conditions which are not detectable through current methods of newborn bloodspot screening for SMA, and are therefore not included in the scope of this HTA.[19-21] Throughout the remainder of this report, 5q-SMA is referred to simply as SMA.

2.2.2 Classification

SMA presents across a continuous gradient of severity divided into functional subtypes. The condition has traditionally been classified into five subtypes, types 0 to IV, based on the typical age of onset, clinical severity, and achieved motor milestones (non-sitters, sitters, and walkers). The classification of these subtypes is briefly outlined in Table 2.1 and is discussed in greater detail in chapter 3 (epidemiology). This classification is typically based on the use of supportive therapy only. Recent advancements in disease-modifying treatments for SMA have changed

the course of the disease for patients within a number of these subtypes, so that outcomes by subtype are now more diverse and may overlap.[2, 3, 5]

Table 2.1 Typical SMA presentation and phenotype*

SMA subtype		Age at onset	Life expectancy	Motor milestones
0		Prenatal	Weeks from birth	None achieved
I		< 6 months	2 years	Non-sitter
II		6 - 18 months	Majority alive at 25 years	Sitter
III	a	18 months - 3 years	Normal	Sitter
	b	3 years - adulthood	Normal	Walker
IV		Adulthood	Normal	Walker

Key: SMA – spinal muscular atrophy.
* In the context of supportive care only; that is, in the absence of disease-modifying treatments.
Sources: Keniath et al.[3], Prior and Leach[5], Wirth et al.[2]

2.2.3 Genotype – phenotype correlation

Given the ability of *SMN2* to produce limited amounts of functional SMN protein, this gene can substitute for the lack of protein produced due to the deletions in *SMN1*.[16-18, 22] The number of *SMN2* copies is inversely associated with disease severity (that is, higher copy numbers of *SMN2* are associated with lower disease severity) and is used a prognostic biomarker for SMA.[2, 17, 18, 22] The quantification of *SMN2* copies is often used as a guide for treatment options in SMA.[2] The following is frequently cited as the most common *SMN2* copy number per SMA subtype:[2, 22]

- type I: two copies of *SMN2*
- type II: three copies of *SMN2*
- type III: three or four copies of *SMN2*
- type IV: four or more copies of *SMN2.*

However, while a correlation between *SMN2* copy number and clinical severity exists, it is not absolute and discordant cases do present.[2, 22] For example, cases of type I SMA can have four *SMN2* copies, and cases of type IV SMA can have two *SMN2* copies.

2.2.4 Diagnosis in the absence of screening

In the absence of newborn bloodspot screening, clinical suspicion of SMA is based on family history or symptomatic presentation (for example, failure to meet motor milestones or difficulty in breathing or swallowing).[1, 5] Symptoms associated with SMA are described in greater detail in chapter 3.

A 2018 international consensus statement on the standard of care for the diagnosis and management of SMA, updated from 2007, presents guidelines for the diagnosis of the condition.[1, 23] Figure 2.1 summarises the stages associated with a diagnosis. Briefly, unless there is familial risk, this process is prompted by clinical suspicion due to symptomatic presentation. A blood draw is taken, and molecular genetic testing is performed to quantitatively analyse *SMN1* and *SMN2.* This is performed using the techniques of multiplex ligation-dependent probe amplification (MLPA), quantitative polymerase chain reaction (qPCR) or next generation sequencing.

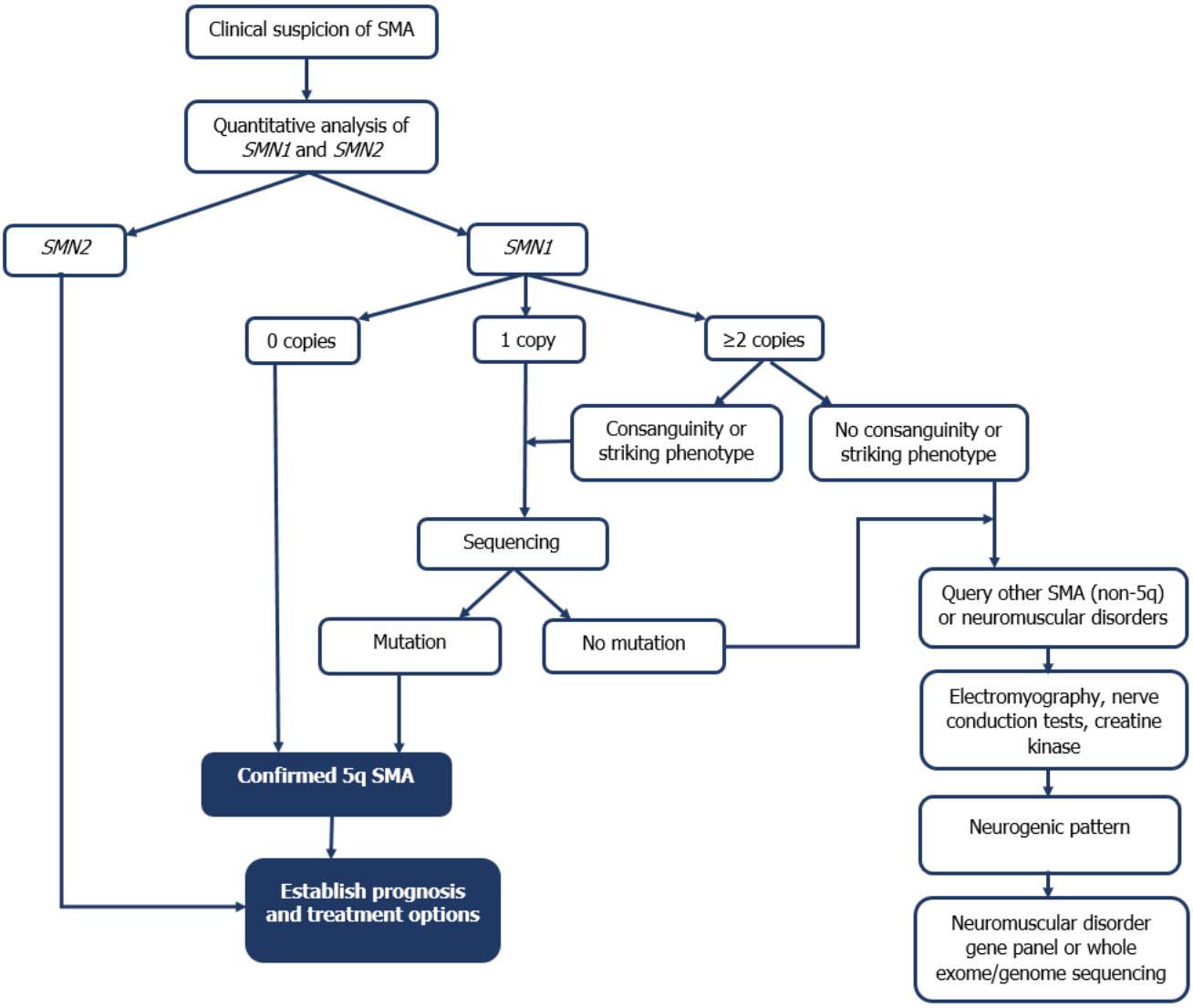
The absence of two full *SMN1* copies (suggesting homozygous deletion of the *SMN1* gene) is indicative of a diagnosis of SMA. If only one full copy is present and the clinical presentation of the child is indicative of SMA, the *SMN1* gene is sequenced to check for point mutations. If both full *SMN1* copies are present, a diagnosis of SMA is highly unlikely, but the international consensus guidelines recommend that *SMN1* gene should be sequenced if there is a clinical presentation consistent with SMA or consanguinity.[1] If sequencing does not indicate a diagnosis of SMA (that is, no relevant pathogenic variants are identified), but clinical features are suggestive of the condition, additional tests such as electromyography and nerve conduction tests may be performed to check for other neuromuscular conditions as part of a differential diagnosis.

In the context of an established diagnosis of SMA on the basis of deletion of *SMN1,* the quantification of *SMN2* copy number offers prognostic value and informs eligibility for certain therapies.[1, 2, 5, 17, 18] While the various quantitative techniques outlined above can be used, MLPA is considered to be the gold standard.[24]

Discrepancies between initial and re-determined *SMN2* copy number have however been highlighted when using this method. A 2019 study repeating MLPA-based quantification in 20 SMA patients identified nine discordant results with seven resulting in lower *SMN2* copy numbers and two being higher.[24] Factors noted to influence the accuracy of MLPA for *SMN2* copy number quantification include the type of equipment used, contamination, obtaining sufficient quality and quantity of DNA, availability and use of appropriate controls, and definition of cut-off values.[24, 25] Accordingly, validation, that is tests of reliability and quality control procedures, should be performed before *SMN2* copy numbers can be broadly used for clinical decisions and interpretation of outcome data. The Department of Clinical Genetics in

Crumlin has validated processes for 1, 2, and 3 *SMN2* copy results. To date, there has not been a clinical need for the centre to validate results indicating four or more *SMN2* copies. However, the centre would perform validation for these results if there was a clinical need to do so.[25] The department participates in international external quality assessment schemes annually.[25]

Figure 2.1 Diagnostic process for SMA



Key: SMA – Spinal Muscular Atrophy, *SMN1 - survival of motor neuron 1, SMN2 - survival of motor neuron 2.*
Source: Mercuri et al.[1]

Diagnostic pathway in Ireland

Similar to the recommendations outlined above, under the current standard of care, patients with SMA in Ireland are identified through symptomatic presentation or, in a minority of cases, family history.[26] As is discussed further in section 2.3.2, the latter

typically involves prenatal testing offered to families with higher risk pregnancies (for example, a previous case of SMA in a sibling). However, it should be noted that not all families will elect to avail of prenatal testing. In terms of symptomatic presentation, as outlined in section 2.2.2, SMA types 0, I, II, and III are associated with the paediatric period while type IV is adult onset. The current diagnostic pathway for each life stage is outlined below.

Paediatric-onset SMA

In paediatric cases of SMA, the diagnostic pathway begins with the recognition of symptoms consistent with the condition by a healthcare professional prompting a referral for diagnostic testing. A blood sample is taken for MLPA analysis to check for deletions in *SMN1* and quantify *SMN2* copy number. MLPA analysis is carried out by the molecular genetics laboratory in the Department of Clinical Genetics at Children's Health Ireland (CHI) Crumlin or, specifically for those seen in the neuromuscular clinic in CHI at Temple Street, by an external provider in Germany. Once diagnosis is confirmed, the child is seen in the neuromuscular service at CHI at Temple Street which acts as the national tertiary referral centre for children with SMA.[(26)] Anti-Adeno-Associated Virus 9 (AAV9) antibody titre levels are quantified to inform treatment planning, as presence of these antibodies may impact the effectiveness of one of the available disease-modifying treatment options. This testing is provided by an external provider in The Netherlands. In the case of a positive result, counselling is provided on the SMA diagnosis and treatment options (outlined in section 2.2.5).

Families of children diagnosed with SMA are referred to the CHI Clinical Genetics Service which provides carrier testing and information on reproductive options. In subsequent pregnancies the parents are offered prenatal testing. Siblings of children with SMA are assessed by a clinical specialist for any potential signs or symptoms of SMA. If there is clinical concern, genetic testing is then undertaken.

Adult-onset SMA

Suspected cases of adult-onset SMA are diagnosed at the local level. Such cases will typically present as a suspected neuromuscular disorder which is investigated further. This may be through the local neurologist or referral to a neurologist with a special interest in neuromuscular conditions. Genetic testing may be undertaken with samples sent to various laboratories depending on local agreements within the hospital (for example, an external provider in Germany); however, there may be variation in the extent to which such testing occurs and the completeness of the genetic panels tested.[(27)]

2.2.5 Treatment

SMA requires multidisciplinary management.[1, 5, 28] The 2018 consensus statement on the standard of care for the diagnosis and management of SMA, outlines guidance for the clinical evaluation and management of the condition.[1, 28] Following diagnosis of SMA, detailed multisystem evaluations of the patient are undertaken and a management plan established and monitored.[1, 5, 28] A range of outcome measures are used to evaluate and monitor patients. Appendix Chapter 2, Table A2.1 outlines some of the common measures used in clinical practice.[1, 28] Evaluation may include:

- growth monitoring
- gastrointestinal function and feeding
- respiratory function
- musculoskeletal function (for example, gross and fine motor skills).

While not mutually exclusive, the management of SMA may be considered in terms of (i) supportive therapy and (ii) disease-modifying treatments.

Supportive therapy

Given the heterogeneity of clinical manifestations of SMA and the development of complications, supportive therapy is guided by the clinical status of the patient.[1, 28] The 2018 consensus statement on the standard of care for the diagnosis and management of SMA provides detailed guidance for assessment and intervention in terms of rehabilitation, orthopaedic management, pulmonary function, nutritional support, home care, and transportation needs.[1, 28] The interventions and goals of management outlined are categorised according to the functional status of the patient (non-sitters, sitters, walkers) and vary widely in terms of gravity and requirements for follow up. For example, respiratory support ranges from invasive ventilation in severe presentations to monitoring and supportive care, when required, in milder forms.

Disease-modifying treatments

Historically, SMA was managed symptomatically through supportive therapies; however, drug treatments now exist which aim to alter disease processes.[2] These therapies may be considered as SMN independent and SMN dependent.[2] SMN-independent therapies include those aimed at neuroprotection and muscle enhancement. To date, no SMN-independent treatments have received licencing approval for SMA,[2, 3] and therefore these will not be discussed further in the context of this HTA.

SMN-dependent therapies include *SMN2* modulators and *SMN1* gene therapy.[2] The clinical indications for these therapies vary depending on patient age and SMA subtype. Three such therapies have been authorised for use by the European Medicines Agency (EMA). Each is briefly discussed below and expanded upon, in terms of mechanism of action, clinical effectiveness and safety, and reimbursement status in Ireland, in chapter 5 (overview of treatments).

SMN2 modulators

Two *SMN2* modulators have been authorised by the EMA. The first EMA authorised drug treatment for SMA was nusinersen (trade name: Spinraza®). It was approved for use in the EU for patients with 5q-SMA in 2017.[29] Nusinersen is given indefinitely by intrathecal injection (that is, into the area around the spinal cord).

The second *SMN2* modulator, risdiplam (trade name: Evrysdi®), received EMA marketing authorisation in 2021.[30] Taken orally once a day, the drug is indicated for the treatment of 5q-SMA patients who have a clinical diagnosis of SMA type I, II or III, or four or fewer copies of *SMN2*.

SMN1 gene therapy

One gene therapy has been authorised for use by the EMA, onasemnogene abeparvovec (OA, trade name: Zolgensma®).[31] It is indicated for patients with 5q-SMA who have pathogenic variants in both copies of the *SMN1* gene and a clinical diagnosis of SMA type I, or patients with 5q-SMA with pathogenic variants in both copies of the *SMN1* gene and three or fewer copies of the *SMN2* gene. It is given as a one-off infusion.

Treatment pathway in Ireland

Paediatric cases

In the case of paediatric patients, once a diagnosis of SMA has been established, the family decides on the treatment course for the child with guidance from the treating clinician at CHI Temple Street.[26] Given the severe form and very limited life expectancy, cases of type 0 SMA are managed with supportive and palliative care, including family counselling. In type I cases, OA is considered the treatment of choice for the majority of applicable cases. For patients with types II and III, nusinersen or risdiplam are typically considered as first-line therapiesy. In both contexts, an application is sent by the treating clinician to the Health Service Executive (HSE) Medicines Management Programme (MMP). In parallel, the clinician informs pharmacy colleagues in Temple Street. In the case of treatment with OA, colleagues in St James's Hospital are also informed.

Where OA is the chosen treatment, a recommendation is typically provided by the MMP within 24 hours of application, with the HSE typically granting authorisation of reimbursement within another 24 hours.[26] A request is then made to the pharmaceutical company who provide the treatment, with a turnaround time of approximately 72 hours for receipt of the product. Overall, within seven to 14 days of diagnosis, treatment is generally available. While the gene therapy is administered in St James's Hospital Dublin, the infant is admitted to CHI Temple Street the day before for pre-procedural tests and for the administration of prednisolone (as part of the treatment protocol). The next day, the infant is transferred to St James's Hospital to initiate gene therapy. Historically, in severely unwell infants, these transfers have been facilitated by the Irish Paediatric Acute Transport Service; however, this is not routinely required and typically the HSE National Ambulance Service is used. A nurse, registrar and the treating clinician accompany the child in transfer. The care episode at St James's hospital generally takes four to five hours, after which the child is transferred back to CHI Temple Street. A ten-day admission at CHI Temple Street typically follows to monitor the child for complications. Once platelet levels have reduced in accordance with the treatment protocol, generally occurring at day seven post-infusion, the child returns home. The child attends CHI Temple Street for monitoring every one to two weeks for the first two to three months. Thereafter, the child attends every four to six months to monitor outcomes and access multidisciplinary (MDT) intervention as required (for example, physiotherapy). Although treatment is centralised to the designated centres in Dublin, an additional neuromuscular clinic is in place in Cork, where children with SMA can attend for follow-up.

Similarly, for nusinersen, an application is made to the MMP with subsequent authorisation being granted by the HSE (collectively taking approximately 48 hours). CHI at Temple Street is the only prescribing centre in Ireland; initial doses are provided at this location, while subsequent doses may be provided at this location or at CHI at Tallaght University Hospital. Unlike OA, it is available in pre-formulated vials, so is generally available from the hospital pharmacy at short notice. For the administration of nusinersen, as per the dosing schedule outlined above, the child is admitted as a day case. Follow-up is typically scheduled with dosing, so both are completed on the same day. The child attends CHI at Temple Street or Tallaght, and meets with other MDT members for evaluation and outcome measure assessments prior to being seen by a clinical specialist. Following evaluation, the intrathecal dose is given and the child remains under observation in the day ward for approximately one hour prior to being discharged home.

As of September 2023, risdiplam is also reimbursed on a named patient basis subject to an application to the MMP by approved prescribers, and authorisation being granted by the HSE. Patients receiving risdiplam do not require admission for

treatment as it is administered daily as an oral solution. The child attends for clinical evaluation to monitor outcomes and to access MDT intervention, as required.

Adult cases

While paediatric-onset SMA cases will transition to adult services for ongoing treatment and monitoring (for example Beaumont Hospital for the ongoing administration of nusinersen), currently there are no SMN-dependent drugs reimbursed for the treatment of adult-onset SMA in Ireland.[27] Treatment is supportive in nature and case-specific depending on the clinical needs of the patient.[27]

2.3 Screening for SMA

Screening for SMA can include carrier screening, prenatal testing, or newborn bloodspot screening. Carrier screening and prenatal testing are briefly described below, followed by newborn bloodspot screening which is the topic of interest in this HTA.

2.3.1 Carrier screening

Molecular genetic testing can establish carrier status for SMA. Similar to the testing process outlined in section 2.2.4, a quantitative analysis of *SMN1* is undertaken to identify heterozygous deletions in the gene (that is, a deletion is present in one allele). Preconception carrier screening has been recommended in the United States for those with and without a family history of SMA;[32] however, the extent to which this occurs in practice is unclear. In Ireland, carrier screening is typically only undertaken in the case of a positive family history and is provided by the Clinical Genetics service at CHI Crumlin.[26] Further detail on the genetic inheritance of SMA and carrier frequency, alongside potential limitations of the process of carrier testing, is outlined in chapter 3.

2.3.2 Prenatal testing

The use of prenatal testing is typically due to both parents being identified as carriers from the identification of an index case of SMA.[3] This service is coordinated by the Clinical Genetics service at CHI Crumlin. Prenatal testing is most commonly performed through the invasive collection of samples from the placenta at weeks 11 to 14 (chorionic villus sampling),[3, 33] from which DNA is extracted and tested for *SMN1* deletions. A non-invasive form of prenatal diagnosis has been available in the UK for three years which involves collecting a blood sample from the mother. This service has been accessed by a number of Irish families.[34]

2.3.3 Newborn bloodspot screening for SMA

The topic of interest in this HTA is population-based newborn bloodspot screening for SMA. While different approaches have been described in the literature (as is outlined in chapter 4), including a variability in the use of second tier tests, the most frequent method of first tier population-based newborn bloodspot screening for SMA is qPCR based assays to detect homozygous deletions in *SMN1* using DNA extracted from dried bloodspot samples. As is discussed further in chapter 4, given the target of these assays is homozygous deletions which account for approximately 95% of all SMA cases, the remaining 5% of cases with a deletion on one allele and point mutations on the other (known as compound heterozygous variants) are not detected by this screening method. Following an initial positive screening test, the newborn requires follow-up testing, often performed using MLPA, to confirm the diagnosis and quantify the number of copies of the *SMN2* gene.

While it may be possible for this confirmatory test to be performed on the original bloodspot sample taken for the purpose of newborn screening; [35] this would be contingent on being able to extract a DNA sample of sufficient quality from the sample. The choice of sample will depend on the outcomes of the verification process (that is, the phase in which the testing method is established, which occurs prior to implementing screening in the population).[25] The screening test cannot distinguish between SMA types. However, prognostic information can be drawn from the *SMN2* copy number (albeit this method is not absolute).

Screening requires co-operation across numerous stakeholders involved in sample collection, sample transport, analysis, reporting of results and ultimately the referral of identified cases to the appropriate clinical pathway.[36] Each of these stakeholders has responsibilities related to their role in the screening programme.[36] While it is the responsibility of the NNBSL to ensure that all screen positive cases are referred to the appropriate clinical care team, reporting standards (for example, the definition of screen positivity applied) and procedures must be agreed between all stakeholder groups prior to implementation. If a decision is made to implement screening for SMA, testing processes, quality assurance practices, and pathways for referral, management and follow-up would need to be developed in consultation with key stakeholders, including clinical specialists, to ensure appropriate end-to-end care for all cases identified within the agreed standards.

Of note, in the event that a decision is made to add SMA to the NNBSP, those with a family history of SMA would continue to be offered prenatal testing where a couple's risk indicates that this is appropriate, in line with current practice.

Commercially available assays

As of August 2023, at least two commercially available assays exist for newborn bloodspot screening of SMA, namely, the PerkinElmer EONIS™ platform, and the Immuno IVD SPOT-it™ screening kit.[37, 38] The EONIS™ kit received FDA authorisation in 2022.[39] Both manufacturers note that the assays are CE-marked (that is, that a product meets requirements for sale in the EEA).[37, 38] Both assays are capable of performing multiplex PCR for the detection of both SCID and SMA, that is, the polymerase chain reaction can be used in these assays to amplify the targets for each of SCID and SMA simultaneously. The EONIS™ kit further allows for the detection of X-linked agammaglobulinemia, a rare immunodeficiency disorder.

Regulation of test kits

In vitro diagnostic medical devices (IVDs) which are intended for newborn bloodspot screening of congenital disorders are subject to EU IVD Regulation 2017/746.[40] 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) now requires 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 newborn babies where failure to detect and treat such disorders could lead to life-threatening situations or severe disabilities'.[41]

Reporting of screen positive results

While the target of the majority of SMA screening worldwide is limited to homozygous deletion of exon 7, some of the international programmes identified had notable exceptions. Programmes in Sweden and Canada (provinces of Alberta, British Columbia, Manitoba, and Ontario) make reference to the number of *SMN2* copies present in second tier screening as qualifiers for a screen positive result.[42, 43] In these programmes, currently, only children with three or fewer (Sweden) or four or fewer (Canada) copies of *SMN2* would be considered screen positive, despite the presence of homozygous deletions of exon 7.[42, 43] This is further discussed in the international practice section below. The ethical implications of this approach are also discussed in chapter 8 (ethical and social considerations).

Treatment algorithms in the context of newborn bloodspot screening for SMA

Treatment options for SMA were historically based on the subtype of the condition as determined by the clinical presentation of the child (see Table 2.1). The emergence of newborn bloodspot screening for SMA means that screened infants will be identified presymptomatically in the majority of cases. It is important to

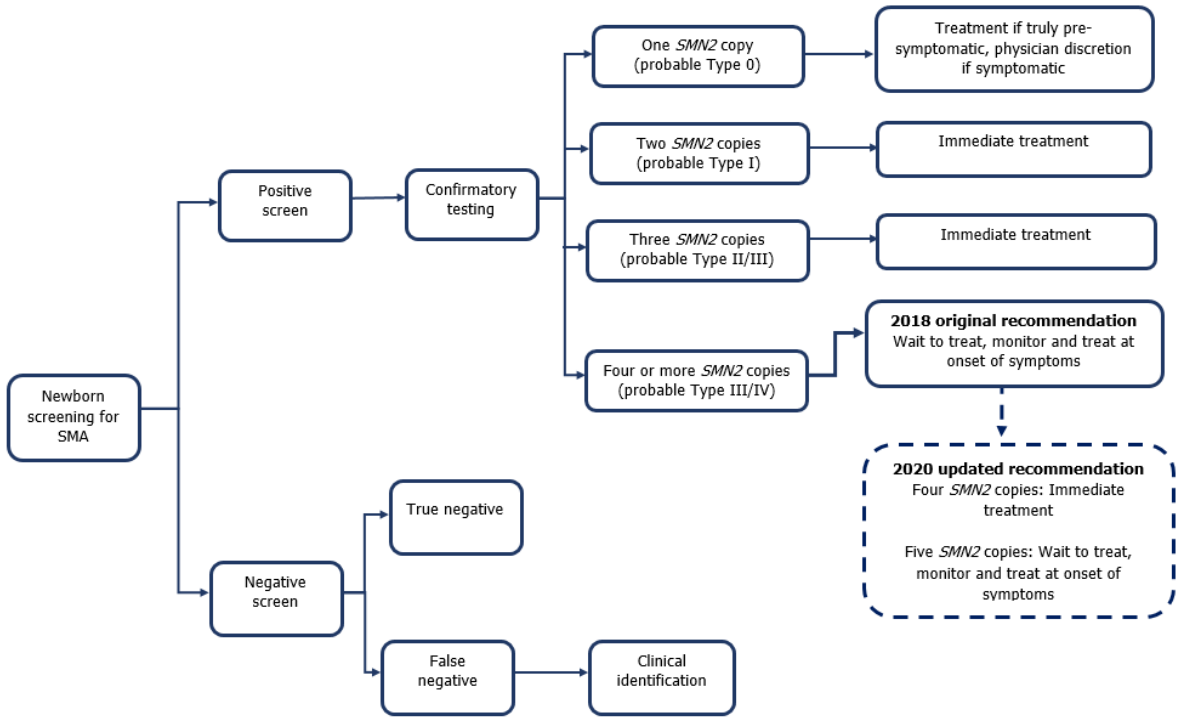
consider how this will impact on the treatment pathways for cases identified. While such treatment pathways will be impacted by the reimbursement protocols in individual countries, two examples identified from the literature are presented below.

SMA Newborn Bloodspot Screening Multidisciplinary Working Group

A consensus-based treatment algorithm for SMA cases detected through newborn bloodspot screening was put forward in the US in 2018 by "The SMA Newborn Bloodspot Screening Multidisciplinary Working Group".[44] This working group consisted of 15 members including clinicians, geneticists with SMA expertise, and patient advocacy representatives, and was supported by the US-based advocacy group CureSMA.[44, 45] It should be highlighted that a number of the members of the SMA Newborn Bloodspot Screening Multidisciplinary Working Group disclosed commercial interest in terms of research funding, advisory/consultancy fees, and or employment status.

The algorithm is presented in Figure 2.2 and is based on the predictive value of *SMN2* copy number following a confirmed diagnosis of SMA. The authors highlight that for type 0 cases, it is highly likely that these children will be symptomatic at birth and hence the consensus is to defer to the medical team to determine if the infant and family would benefit from disease-modifying treatment based on clinical status. The 2018 algorithm recommended that those with two *SMN2* copies (probable type I) or three copies (probable type II or III) should be offered immediate treatment, and those with four or more copies (probable type III or IV) should not receive immediate treatment but should be monitored carefully for the first presentation of symptoms. However, this recommendation was updated in 2020.[46] The updated recommendation recommends the immediate treatment of all infants diagnosed with SMA through newborn bloodspot screening who have four or fewer copies of *SMN2*. This recommendation was based on an extrapolation of benefits observed in a single arm trial of nusinersen for patients with two or three *SMN2* copies to those with four copies.[46] The recommendation to not immediately treat those with five *SMN2* copies, and instead to closely monitor such patients, did not change. It was further acknowledged that assays can have difficulty in quantifying precise numbers of *SMN2* at the higher end of the scale and so follow-up should be performed with a laboratory capable of precise estimation.

Figure 2.2 US group consensus recommendations (2018 and 2020) on treatment of SMA in the context of newborn bloodspot screening



Source: Newborn Bloodspot Screening Multidisciplinary Working Group 2018 and 2020[44, 46]

Ontario newborn bloodspot screening for SMA: testing and follow-up recommendations

Aligning with the implementation of newborn bloodspot screening for SMA in Ontario Canada, a group of paediatric neuromuscular disease and newborn bloodspot screening experts were convened to establish, by consensus, a standardised post-referral evaluation pathway for infants with a positive screen result.[47] A series of teleconferences and a final one day face-to-face meeting were used.

Consensus was reached that infants with homozygous deletion of *SMN1* and four or fewer copies of *SMN2* would be classified "screen positive" and referred to a regional treatment centre. A trained genetic counsellor or nurse would contact the infant's family by telephone, and they would be directed to the closest paediatric hospital, have blood sent for confirmatory SMA testing, and meet with a paediatric neuromuscular specialist to discuss the potential implications of the test result. Following diagnostic confirmation, and determination of *SMN2* copy number, infants and their families would be assessed by a paediatric neuromuscular specialist at which time the family would have an opportunity to discuss treatment options and

standard of care guidelines that are followed at all Ontario Paediatric Neuromuscular clinics. Baseline functional assessments would also be performed.

At the time of the consensus recommendations, nusinersen was the only disease-modifying treatment for SMA reimbursed in Canada. The following treatment guidelines based on *SMN2* copy number were recommended by the group:

- One *SMN2* copy (likely type 0 SMA): recommended immediate evaluation. Given the potential severity of this congenital-onset form of SMA which could include the need for mechanical ventilation, the paediatric neuromuscular physician and family would discuss potential treatment options.
- Two or three *SMN2* copies: given the evidence for rapid and irreversible loss of motor neurons, recommended for immediate initiation of disease-modifying treatment prior to any clinical symptom onset (recommendation is concordant with Ontario's Exceptional Access Program reimbursement criteria for nusinersen). Ongoing surveillance through structured measures dependent on age (see Appendix Chapter 2, Table A2.2).
- Four *SMN2* copies: neuromuscular assessment and nerve conduction studies recommended as type I or II can present with four copies. Any clinical sign of SMA on neuromuscular examination (for example, weakness, hypotonia, hyporeflexia) or neurophysiological evidence would prompt initiation of disease-modifying treatment. If no signs of SMA then treatment would not be initiated and the child would be seen every three months until 12 months of age with structured outcome measures dependent on age (see Appendix Chapter 2, Table A2.3). After this time point, the intervals between appointments would be extended and age appropriate outcome measures would be used, with the child scheduled to be seen at 18 months, 24 months, and annually from there on.

It should be highlighted that a number of the authors of these recommendations, disclosed commercial interest in terms of research funding and or advisory or consultancy fees.

Possible Irish treatment pathway in the context of newborn bloodspot screening

As highlighted, any decision to implement newborn bloodspot screening for SMA would require the establishment of a working group of stakeholders to outline the associated pathways.[35] Given the evolving evidence base, a treatment pathway would be influenced by the most up-to-date evidence with respect to treatment effectiveness and the access arrangements for the relevant treatments at that time (that is, the reimbursement arrangements in place), in addition to factors relating to

patient experience. However, at a high level for the purposes of this HTA, the following treatment pathway has been outlined by clinical specialists as a possible course of action:[26]

- Following confirmatory testing and quantification of *SMN2* copy number, the clinician would discuss treatment options with the family.
- For those with prenatal onset type 0 SMA, the current treatment pathway of supportive and palliative care would be maintained.
- For those who become symptomatic, it is anticipated that the usual treatment pathway will be followed.
- For those who are asymptomatic with three or fewer copies of *SMN2*, provided AAV9 titres do not prohibit, immediate treatment with OA through the pathway outlined in section 2.2.5 is considered to be the most likely strategy.
    - Should AAV9 titres prohibit immediate treatment, it is likely, given the age of the infant, that titre presence would be reflective of maternal causes.[48] The child would receive a bridging therapy (most likely nusinersen) until the AAV9 titres reduce. At this point, the treatment would be changed to OA.
- For asymptomatic children with four or more copies of *SMN2*, a watchful waiting strategy could be advised. The child would undergo detailed clinical evaluation including nerve conduction studies. If no signs of the disease are identified, the child would be followed-up by a clinical specialist in SMA at three-monthly intervals for the first 12 months and six-monthly thereafter.
    - Treatment initiation would be at symptom onset and based on SMA type classification, with the pathway followed as per the current standard of care of clinical identification outlined in section 2.2.5.
- As per the current standard of care, genetic counselling would be provided, carrier testing offered to parents, and prenatal testing offered for any subsequent pregnancies. Siblings of SMA cases would undergo clinical evaluation by a specialist, with any signs of disease prompting genetic testing.

2.4 International practice in newborn bloodspot screening for SMA

To provide an overview of current international practice regarding newborn bloodspot screening for SMA, a scoping search was performed up to August 2023 which examined countries deemed to be of most relevance to Ireland, including those in the European Economic Area, the United Kingdom, the United States, Canada (provinces), Australia (regions) and New Zealand. A targeted grey literature search (for example, national public health organisations, and the websites of

governmental departments and relevant agencies), was performed. Thirty-four countries were assessed, with a number including specific territories or regions (Australia and Canada).

A summary of the findings of this review is presented in Table 2.2, followed by detailed findings for each specific country. As outlined in Table 2.2, of the 34 countries that were examined, newborn bloodspot screening for SMA was fully nationally implemented in eight countries, regionally implemented in four countries, under implementation nationally in one country, being piloted in seven countries, and under review in two countries.

Table 2.2 Overview of countries identified as having screening for SMA in place, undergoing implementation, undergoing pilot, and under review[†]

Country/Provence	Level of implementation
Austria	Full implementation
Australia (regions)	Regional implementation
West Australia	Full implementation
South Australia/Tasmania	Under implementation
Queensland	Full implementation
New South Wales/ Australian Capital Territory	Full implementation
Victoria	Pilot or implementation planned for 2023
Belgium	Full implementation
Canada (provinces)	Regional implementation
Alberta	Pilot
British Columbia	Full implementation
Manitoba	Pilot
Ontario	Full implementation
Quebec	Under review
Saskatchewan	Pilot
Croatia	Full implementation
Czech Republic	Pilot
Denmark	Full implementation
Estonia	Pilot
France	Pilot

Country/Provence	Level of implementation
Germany	Full implementation
Hungary	Pilot
Italy	Regional implementation
Latvia	Pilot
The Netherlands	Full implementation
New Zealand	Under review
Norway	Full implementation
Poland	Full implementation
Portugal	Pilot
Spain	Pilot
Sweden	Under implementation
United Kingdom	Under review
United States	Regional implementation*

† For the purposes of this review, a pilot study was defined as a small-scale preliminary study. The study may or may not precede a decision to implement, and may or may not use the methods or procedures used at a regional or national level implementation (for example, an SMN2 threshold).
* A recommendation had been made for national implementation, however not all states have implemented screening for SMA as of August 2023.

Austria

In June 2021 pilot screening for SMA was introduced.[49] Since then SMA has been added to the country's national newborn bloodspot screening programme.[50]

Australia

The jurisdictions of New South Wales, the Australian Capital Territory, and Western Australia currently offer newborn bloodspot screening for SMA.[51] In the jurisdictions of Queensland, the Northern Territory, and South Australia, pilot programmes have commenced. In the jurisdiction of Victoria, a pilot programme or implementation has been planned for 2023.

Belgium

Following a three year pilot in southern Belgium (Wallonia and Brussels), SMA screening transitioned into the official newborn bloodspot screening programme in March 2021.[52] Northern Belgium (Flanders) correspondingly made a political commitment to include SMA in their official programme and SMA screening began in 2022.[52, 53]

Canada

Seven of ten Canadian provinces were identified as having newborn bloodspot screening for SMA to some extent. Of note, the newborn bloodspot screening programmes of Alberta, British Columbia, Manitoba, and Ontario do not consider homozygous deletions of *SMN1* with five or more copies of *SMN2* to be a positive result.[42]

Alberta

Beginning in February 2022, infants are screened for SMA through a pilot programme funded by Muscular Dystrophy Canada.[54] The screening test will become part of Alberta's newborn bloodspot screening programme after the pilot programme is completed.[54]

British Columbia

All infants born after 30 September 2020 are screened for SMA following a programme expansion which also included the addition of SCID and biotinidase deficiency.[55]

Manitoba

Beginning in June 2022, all dried bloodspots received for newborn bloodspot screening at the Manitoba Newborn Screening Program will be screened for SMA as part of a two year pilot programme.[56]

Quebec

In November 2021, the Canadian HTA organisation, Institut national d'excellence en santé et services sociaux (INESSS), published an assessment of the suitability of neonatal screening for SMA.[14] Consequently, INESSS recommended the addition of SMA to the neonatal screening programme of Quebec.

Ontario

Screening for SMA started in January 2020 as a pilot program.[57] SMA was officially added to the newborn bloodspot screening panel in Ontario in July 2020.[57]

Saskatchewan

A two-phase pilot started in February 2022, which involves external validation prior to permanent addition to the newborn bloodspot screen panel.[58] The pilot includes SMA, SCID, haemoglobinathopies, and congenital cytomegalovirus.[58]

Croatia

Newborn bloodspot screening for spinal muscular atrophy has been in place in Croatia since March 2023.[59]

Czech Republic

A nationwide pilot programme has been launched in the Czech Republic, which has expanded neonatal screening to include SMA and SCID.[60]

Denmark

The Minister for Health of Denmark announced that SMA will be added to the countries existing newborn bloodspot screening programme in 2023.[61] The decision was made on the basis of a recommendation from the Danish health authority, Sundhedsstyrelsen.[61] As of January 2023, all newborn heel prick samples are screened for SMA.[62]

Estonia

A pilot programme to screen for SMA commenced in 2022.[63]

France

The DEPISMA project, which started in late 2022, launched by AFM-Téléthon, in collaboration with the University Hospitals of Strasbourg, the University Hospital Centre of Bordeaux, and the Grand-Est and Nouvelle Aquitaine regional health agencies, aims to assess the feasibility of national screening for SMA.[64] The project will run for two years.[64]

Germany

Germany launched an SMA pilot programme in January 2018. Following two years of this programme, the Federal Joint Committee for Health gave a positive recommendation for the inclusion of SMA on the newborn bloodspot screening programme in April 2021.[65]

Hungary

Following a decision by the National Centre of Public Health, an SMA research programme began in November 2022.[66]

Italy

SMA screening in Italy was first implemented as a two-year pilot study in 2019 covering hospitals in the Lazio and Tuscany regions.[67] Screening has continued in these regions beyond the pilot programme.[67] The Puglia region placed SMA screening into regional law (as a pilot) in April 2021.[68]

Latvia

A pilot study was performed in Latvia between February and November of 2021 and encompassed all the country's maternity departments and hospitals.[69] This pilot was followed by strong recommendation to add SMA to the newborn bloodspot screening programme;[69] however, it is unclear as to whether it has since officially been added to the national programme.

The Netherlands

The Health Council of the Netherlands recommended that the country screen for SMA in 2019.[70] Following the results of a 2020 feasibility study, screening for SMA was introduced in the Netherlands as part of the national newborn bloodspot screening programme in June 2022.[71]

New Zealand

According to minutes for the New Zealand National Screening Unit meeting on 27 July 2022, the introduction of SMA screening is under review.[72]

Norway

In 2020, the Ministry of Health and Care Services received an application to consider the expansion of the newborn bloodspot screening programme to include SMA.[73] SMA was subsequently added to the national screening panel in September 2021.[73]

Poland

Screening for SMA in Poland was introduced initially as part of a pilot programme and gradually increased to screen all infants born in the country since March 2022.[74]

Portugal

A pilot SMA screening programme began in October 2022,[75] following the publication of a white paper on the subject in July 2021 by the European Alliance for Newborn Screening in SMA.

Spain

A pilot SMA screening programme was announced in February 2021 by the Valencia University hospital.[76]

Sweden

Newborn bloodspot screening for SMA was approved for inclusion in the country's national screening programme, and is awaiting the introduction of regulations which

are expected by the end of summer 2023.[43] Notably, the report which informed the decision to implement screening recommends that only those born with three or fewer copies of *SMN2* be considered screen positive.[43]

United Kingdom

SMA was examined in 2018 by the UK National Screening Committee (NSC) to determine its suitability for addition to the national newborn bloodspot screening programme.[77] At this time the condition was not recommended. At the time of the analysis, the committee considered that there was insufficient evidence to show how effective a screening programme would be and the best way to support positive results was not known.[77] Since then, the UK NSC has recommended that an 'in-service evaluation' should take place and that a new cost-effectiveness model for the UK screening context be developed. Separately, a pilot study by Oxford University, and funded by the pharmaceutical industry and academia, is currently underway as of March 2022, and is expected to be completed by March 2025.[78]

United States

SMA was added to the Recommended Uniform Screening Panel in 2018.[79] According to the Health Resources and Services Administration government website, 48 states in the US currently screen for SMA as part of their respective newborn bloodspot screening programmes.[80]

2.5 Discussion

The purpose of this chapter was to describe the key elements of the technology under consideration (that is, newborn bloodspot screening for SMA). It should be emphasised that newborn bloodspot screening for SMA would constitute an addition to an existing national screening programme. In this way, it is important to consider how the screening pathway for SMA including the screening test, referral routes, and diagnostic and treatment pathways would be embedded within the existing programme.

The NNBSP currently screens for nine conditions. Screening for SCID was given a positive recommendation by NSAC, received approval for addition from the Minister for Health in January 2023, and will further be added to the programme.[11] The 2022 HIQA HTA completed to support this recommendation, identified that investment in new equipment, resourcing, and training was required for the NNBSL to facilitate addition of SCID to the NNBSP. This investment largely centred on PCR-based analysis involving the same equipment required to facilitate SMA screening. As outlined in section 2.3.3, commercial assays have multiplex capability for dual testing of both SCID and SMA. As such, efficiencies would likely arise were both SCID and

SMA testing to proceed; such efficiencies are discussed in further detail in the budget impact and organisational implications chapters.

A defined diagnostic pathway for SMA exists in Ireland. Under the current standard of care (that is, identification predominantly based on symptomatic presentation), cases of SMA are identified across infancy, early childhood, later childhood, and into adulthood. The screening test cannot differentiate between SMA subtypes and hence the introduction of newborn bloodspot screening for SMA would imply that all cases of SMA resulting from homozygous deletions in *SMN1* would be detected in early infancy. This has implications for the treatment pathway, whereby cases of SMA who would not otherwise present until later childhood or even adulthood would be identified significantly earlier.

In the context of a positive screening recommendation a proportion of SMA cases would likely accrue benefit in terms of receiving treatment before, or in the early stages of, neurological impairment. However, there is the potential for over-diagnosis, a change in treatment strategy, and or inefficient resource use in children who remain asymptomatic and would not otherwise present until late childhood or adulthood. Such factors are contingent on the definition of screen positivity adopted, decision-making regarding the treatment pathway in the context of a newborn bloodspot screening programme, the reimbursement criteria for pharmaceutical intervention, and the use of watchful waiting strategies. This appears particularly pertinent in those with higher *SMN2* copy numbers for whom the disease course is associated with greater clinical uncertainty.[47, 81] As is detailed further in chapter 3 (epidemiology and burden of disease), while a correlation exists between this biomarker and disease severity, it is not absolute.[22] For example, type I SMA is most frequently associated with two *SMN2* copies, however, cases with four or more copies have been documented. Type IV SMA is typically associated with four or more copies but cases with lower copy numbers do present. It is notable that, contrary to practice in many programmes, screening programmes in Sweden and Canada (Alberta, British Columbia, Manitoba, and Ontario) have included a criterion for the definition of a case of SMA that is based on *SMN2* copy number.[42, 43] Under this criterion, only cases that are positive on PCR-based testing and also have three or fewer (Sweden) or four or fewer (Canada) copies of *SMN2* are considered to meet the definition of SMA for the purposes of screening.[42, 43] That is, infants with homozygous deletions in *SMN1*, thereby fulfilling SMA diagnostic criteria, but who had higher *SMN2* copy numbers, are not reported as screen positive and are therefore not carried forward in the screening pathway. These decisions were made in light of the programmes finding an uncertain natural history of patients with higher *SMN2* copy numbers and that the appropriate treatment for these individuals is unclear.

Newborn bloodspot screening for SMA was noted to be implemented across a number of countries in Europe, alongside Canada and the United States. The implementation of such screening programmes has been associated with the publication of several studies which provide detail of elements such as algorithms used and effectiveness outcomes. These are detailed in chapter 4 of this report. Given the relative recency of defined testing methods and disease-modifying treatments, it is unsurprising that many programmes are in pilot or regional phases of implementation.

A 2021 international survey of experts in countries with (n = 9) and without (n = 76) newborn bloodspot screening for SMA up to December 2020, examined actual and foreseen obstacles to its adoption and or implementation with a number of commonalities reported across both groups.[7] These included lacking financial resources, limited health economic data or cost-benefit analyses, limited long term follow-up data on the effectiveness of pre-symptomatic treatment, and limited resources and support from government. In countries without newborn bloodspot screening, additional factors included the need for clear professional consensus for treatments at national and international levels, alongside clear guidelines and recommendations, especially for those with four or more *SMN2* copies. Thirty-seven respondents reported plans for establishing newborn bloodspot screening for SMA, indicating the potential for an increase in the number of countries screening in the coming years. It should be noted that this survey is associated with a number of limitations including the coverage attained (87 experts from 82 countries of 152 countries contacted), the surveying of clinical stakeholders involved in SMA care as opposed to those responsible for decision-making on screening, a limited description of survey methods used (for example, question generation), and a declaration of competing interests including consultancy and funding from industry partners by the lead authors.

Collectively, the technology under consideration within this HTA, that is newborn bloodspot screening for SMA, appears to be associated with an established means of screening in terms of a clinical test, a defined clinical pathway in terms of diagnosis in Ireland, and has been implemented across a number of countries internationally. SMA represents a rare, genetic condition; however, there is heterogeneity across subtypes in terms of the age of clinical onset and disease severity. While the majority of cases identified through screening may benefit from earlier detection and treatment, there is potential for over-diagnosis and a change in treatment strategy for some cases. The following chapters will focus on the epidemiology and burden of disease associated with SMA, the clinical effectiveness of newborn bloodspot screening for SMA, the availability and outcomes of disease-modifying treatments, the cost-effectiveness and resource implications of screening, and the organisational, ethical and social considerations relevant to screening for SMA.

3 Epidemiology and burden of disease

Key points

- Spinal muscular atrophy (SMA) is a genetic neuromuscular condition characterised by a deficiency in spinal motor neuron (SMN) protein; this deficiency causes progressive damage to nerves leading to muscle weakness and atrophy.
- SMA is categorised clinically into five distinct subtypes (type 0 to type IV). Type 0 is the most severe form of SMA with a prenatal onset and a life expectancy of days to weeks. Of the remaining subtypes, type I SMA represents the most severe form with a reducing severity moving up the SMA subtypes. This reduction is noted in terms of physical impact, quality of life, and caregiver burden.
- The aetiology of SMA involves an autosomal recessive inheritance pattern, where in the majority of cases each parent is a carrier of the associated genetic pathogenic variant. Where both members of a couple are carriers, each of their children has a one in four chance of having SMA.
- From the Irish context, of 25 paediatric cases with data on age at diagnosis provided by Children's Health Ireland (CHI) at Temple Street, the median age for type I was six months (range 0 to 7.9 months), type II was 19 months (range 12 to 24 months), and type III was 144 months (range 42 to 192 months). These cases all presented between 2015 and 2022.
- Estimates of the incidence of SMA vary internationally. This variation may be due to geographical differences, testing approaches, or challenges in the estimation of rare diseases generally. International data suggest an incidence of types I to IV SMA of 1 in 8,932 (95% prediction interval (PI) 1 in 24,423 to 1 in 4,394). This is equivalent to an average of 6.5 cases (95% PI: 2.4 to 13.2) a year in Ireland, based on approximately 58,000 births.
    - Irish data from which SMA incidence could be estimated were available for a five-year period between 2018 and 2022. These data suggest an incidence estimate for SMA diagnosis of 1 in 12,211. While care of children with SMA in Ireland is centralised, care of adult patients is not. This means that some adult cases may not be included in these figures and the incidence could be underestimated.
    - Of note, there are challenges in obtaining reliable estimates of type 0 (due to early mortality) and type IV (due to mild disease presentation)

SMA in particular. However, these subtypes are typically considered to represent a small minority across the SMA subtypes.

- The proportions of SMA cases that are types I to IV were estimated through a meta-analysis of identified studies. Type I was estimated to comprise the largest proportion of patients at 55.3%, followed by type II (23.3%), type III (20.4%) and type IV (1.0%).
- Clinical subtyping (that is, classification of patients as types 0 to IV) is determined by the emergence of symptoms and the age at onset. Therefore, the introduction of newborn bloodspot screening for SMA would effectively remove clinical subtyping. In this context, prognosis, and subsequent treatment decision-making, would be reliant on genetic-phenotype correlation (using the survival motor neuron 2 (*SMN2*) gene copy number of a patient as a biomarker).
- A meta-analysis was undertaken to indicate the likely clinical course for individuals based on *SMN2* copy number using historical data from patients presenting clinically with symptoms.
    - Those with up to three copies of *SMN2* represented 85.0% (95% CI: 65.3% to 94.5%) of patients with SMA. Of these patients, 99.8% (95% CI: 98.8% to 100%) were estimated to present with types I to III SMA.
    - Those with four copies of *SMN2* represented 11.1% (95% CI: 4.3% to 19.9%) of patients with SMA. Of these patients, 94.4% (95% CI: 82.8% to 99.2%) were estimated to present with types I to III, with the remainder presenting with type IV SMA (5.6%, 95% CI: 0.8% to 17.2%).
    - Among those with five or more copies of *SMN2*, the likely SMA type is subject to substantial uncertainty due to the very small number of cases with five or more copies that have presented clinically in the absence of screening. However, the available evidence suggests that these patients would have milder SMA.
    - As identification was primarily based on symptomatic presentation, the percentages of patients with higher copy numbers may be underestimated given the evidence that these individuals typically experience a milder disease course and may be less likely to present in clinical practice.
- While lower copy numbers of *SMN2* are typically associated with more severe SMA subtypes (and, conversely, higher with less severe), this correlation is not

absolute. There is, for example, a proportion of patients with type I SMA who have four or more copies of *SMN2*, and vice-versa, a proportion among type IV with two or three copies. On both ends of the spectrum this has implications in terms of the treatment and management that is likely to be offered.

The purpose of this chapter is to describe the epidemiology and burden of disease associated with spinal muscular atrophy (SMA). The chapter outlines the aetiology of the condition, followed by the incidence, genotype-phenotype correlation, clinical presentation, and natural history and burden of disease. International data and data from 55 children born with SMA in Ireland between 2001 and 2023 are included where relevant; the latter data were obtained from a clinical database at Children's Health Ireland (CHI) at Temple Street.[82] These data were supplemented with data from the Department of Clinical Genetics at CHI at Crumlin for patients diagnosed from 2015 to 2023. As this department accepts samples for diagnostic testing of adult patients, the Crumlin data also included some results for patients diagnosed as adults (that is, probable type IV SMA). As care for patients with adult SMA is not centralised in Ireland, it was not feasible to source incidence or prevalence of type IV (that is, adult onset) from Irish clinicians given the rarity of the disease.

Where necessary, to obtain estimates for the budget impact analysis (chapter 6), *de novo* analyses of international data were undertaken by the HIQA evaluation team. Two meta-analyses of data collated from two published literature reviews of incidence rates and survival motor neuron 2 *(SMN2)* gene copy number distributions in SMA were undertaken using a generalised linear mixed methods (GLMM) approach.[21, 22] In the case of the *SMN2* copy number meta-analysis, studies providing relevant data identified by the evaluation team throughout the course of this HTA were also included. Prediction intervals (PI) are presented to quantify the uncertainty around the resulting estimates from these analyses. These intervals outline a range where a future additional data point may lie given the previous observed data points. All analyses were completed in *R* (version 4.1.0) using the 'metafor' package.

3.1 Aetiology

SMA is caused by a lack of survival motor neuron (SMN) protein. SMN is an essential protein for all cells for the function of splicing; that is, part of the process where genetic material is converted into a final protein product.[2, 16-18] While essential to all cells, reduced SMN levels appear to primarily affect neuromuscular junctions innervated by alpha motor neurons.[2, 16-18] Hence, a lack of functional SMN leads to degeneration, and irreversible loss, of alpha motor neurons in the anterior horn of the spinal cord.[2, 16-18] This results in progressive muscle weakness and wasting which affects the ability to control movement and, in more severe forms, can impact a child's ability to feed and breathe.

Across all SMA cases there is a bi-allelic disruption of the survival motor neuron 1 *(SMN1)* gene (that is, both versions, or alleles, of the gene are affected), which impedes the production of SMN. Over 108 different pathogenic *SMN1* variants have

been described.[2] It is estimated that 95-98% of SMA cases are caused by homozygous deletion of the *SMN1* gene on chromosome 5 which results in a homozygous loss of *SMN1* exon 7 or exons 7 and 8 (that is, deletions are present in both alleles).[2, 3, 5] The remaining 2-5% of cases present with compound heterozygous variants (that is, there is a deletion in one allele and the second allele has different pathogenic variant).[3] Clinical SMA cases are distinct from carriers in that there is disruption in both alleles, whereas carriers have a disruption of one allele only.

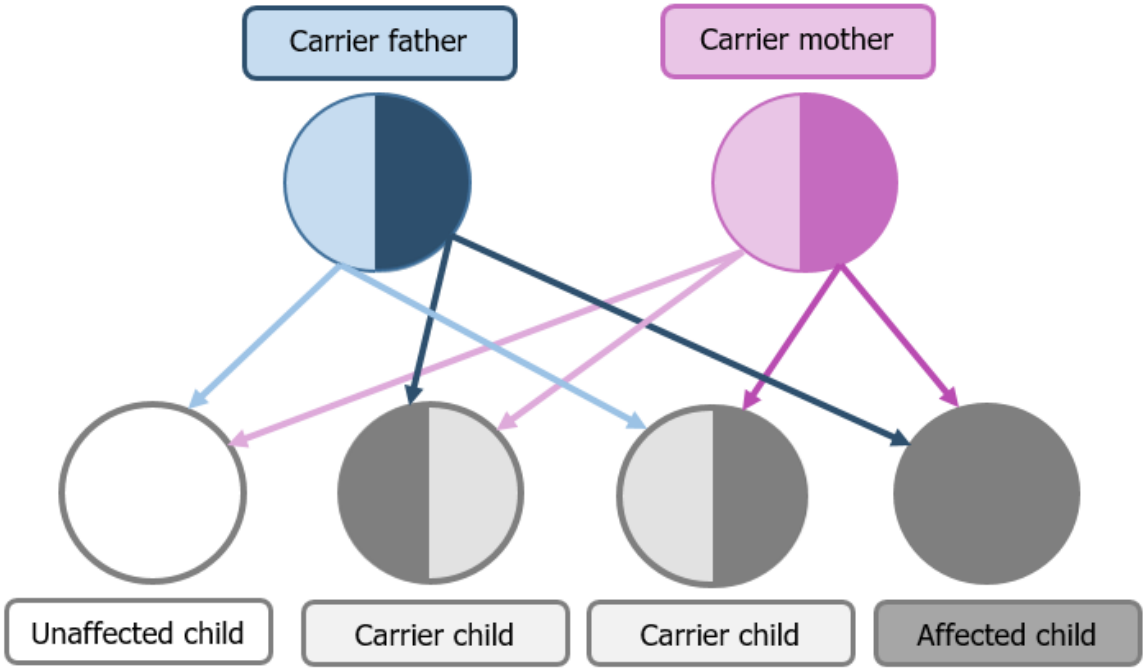
While the majority of functional SMN is produced through *SMN1,*[3, 17, 18] several different versions of the SMN protein are also produced by the *SMN2* gene which is also located on chromosome 5. However, only one form is of full size and functional.[3, 5, 17, 18] The more *SMN2* gene copies a person has, the more SMN protein they produce and hence the number of *SMN2* copies present acts as a modifier of functional SMN production.[16-18, 21] Typically, humans have one or two copies of the *SMN2* gene but some people have up to eight copies.[17, 18]

3.1.1 Inheritance pattern

The vast majority of cases are inherited in an autosomal recessive fashion.[2, 5] As outlined in Figure 3.1, autosomal recessive inheritance means that the mutated gene occurs on one of the 22 non-sex chromosomes ('autosomal') of each carrier parent and a child is clinically affected when both parents pass on their mutated gene ('recessive'). This kind of inheritance equates to a one in four chance that the child will have SMA, a one in two chance that the child will be a carrier and a one in four chance that they will neither have SMA nor be a carrier.

Approximately 2% of SMA cases are considered to have a *de novo* pathogenic variant in one allele; in these instances, only one parent is a carrier.[2, 5]

Figure 3.1 Autosomal recessive inheritance pattern



3.1.2 Carrier status

The process of carrier testing is outlined in section 2.3.1. Carrier status for SMA may be divided into four main *SMN1* genotype categories as outlined in Figure 3.2, B) to E).[21] The most common non-carrier genotype (A) involves a normal copy of *SMN1* on each chromosome, and therefore has two copies of *SMN1* in total. A rarer non-carrier genotype (not illustrated in Figure 3.2) involves two functional *SMN1* copies on one chromosome and one functional copy on the other, that is, three copies of *SMN1* in total. The most frequent carrier state (B) is the '1 + 0' genotype; this form means that there is one normal copy of *SMN1* on one chromosome and no functional copy on the other chromosome (1 copy of *SMN1* in total). The '2 + 0' genotype (C) exhibits two functional *SMN1* copies on one chromosome and none on the other. The remaining genotypes, '1 + 1D' (D) and '2 + 1D' (E), are considered to be rare and involve having one or two functional copies on one chromosome and a non-functional copy on the other. The identifier 'D' in these genotypes denotes the presence of a point mutation or microdeletion as the pathogenic variant.

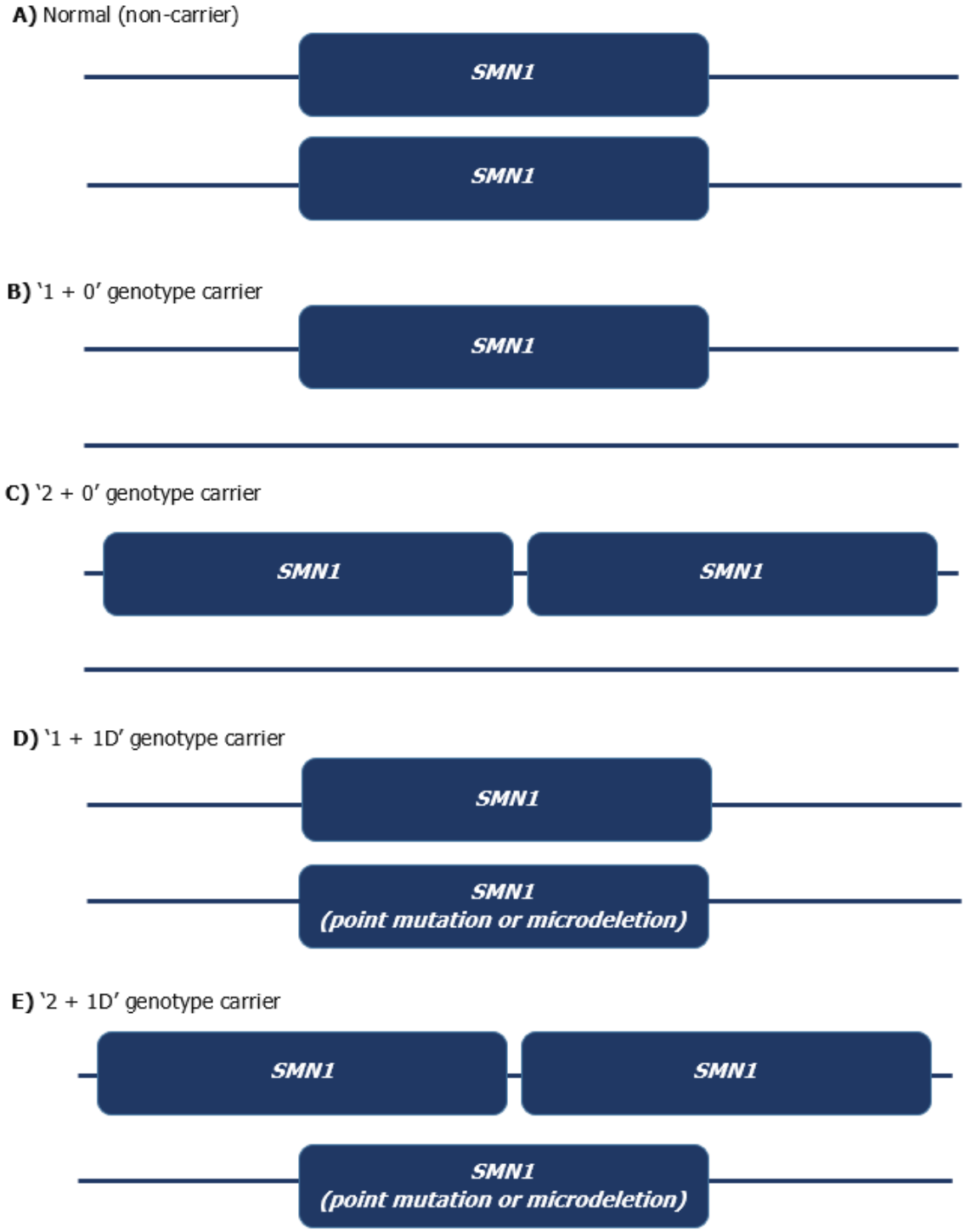
Tests such as multiplex ligation-dependent probe amplification (MLPA) which measure *SMN1* copy number do not provide a definitive carrier/non-carrier result for every individual tested. They can confirm carrier status for the most common '1 + 0' carrier genotype, since only one copy of *SMN1* is present. The '2 + 0' genotype, present in approximately 5 to 8% of the population, can evade carrier testing given that two copies of *SMN1* will be detected without distinguishing where they are

placed.[5, 21] Also, they cannot detect the rarer 1D pathogenic variants. Therefore, where two copies of *SMN1* are detected during carrier testing, it is generally not possible to exclude carrier status. Carrier testing is still very helpful, since a carrier risk figure may be calculated which considers family history of clinical SMA and the results of any genetic testing done in other family members. Risks can be estimated both from an individual perspective (risk of being a carrier) and for a couple (risk of having a child affected with SMA). Collectively, the potential for *de novo* pathogenic variants, gene conversion events, and asymmetrical carrier genotypes mean the efficacy of carrier testing using routine methods is limited. That is, cases of SMA can still occur even if carrier testing does not suggest a risk. If not detected through carrier testing, these cases would still be identified through the proposed newborn screening programme (detection of homozygous deletion of *SMN1)*.

While not within the scope of the current HTA, some jurisdictions, such as Israel, offer testing to identify SMA carriers as part of a population-based screening programme.[83] Carrier screening can be carried out either pre conception or during pregnancy and is separate to newborn bloodspot screening for SMA.

Were newborn bloodspot screening for SMA to be introduced, the earlier identification of patients with SMA may lead to an increased number of their family members availing of carrier testing or availing of it earlier.

Figure 3.2 SMA carrier genotypes



Key: SMA – spinal muscular atrophy, *SMN1 - survival of motor neuron 1*
'D' denotes point mutation or microdeletion
Source: Verhaart et al.[21]

Carrier frequency

A consideration of carrier frequency is relevant to this HTA, given its relationship with SMA incidence and the potential for earlier and increased carrier testing if screening for SMA were to be introduced. Given the autosomal recessive nature of SMA, carrier frequency likely varies across populations.[21] Populations who are geographically isolated or have high rates of consanguineous unions (that is, between individuals who are related) can have particularly high carrier frequencies.[21]

A 2017 literature review sought to summarise the carrier frequency of SMA across different ethnic groups.[21] The authors noted that most studies have been conducted outside of Europe, varied in terms of the methods used to determine carrier status, and were conducted in varying population sizes (for example, small ethnic groups versus population-based). Collectively, across all studies included, the carrier frequency was estimated at 0.019 (1:52). The carrier frequency by ethnic group is presented in Table 3.1. The estimates of carrier frequency will inevitably be approximate; this is due to the limitations in the methods used to derive the estimates, which require mathematical modelling in some cases, and the ability of some genotypes to evade carrier testing. For example, it is highlighted that the lower carrier frequency seen in certain groups (for example, Black Sub-Saharan) is likely due to the presence of a higher frequency of carrier genotypes evaded by traditional carrier testing (for example, '2+0' in Figure 3.1 above).[21]

Table 3.1 Carrier frequency across ethnic groups

	Population	Carriers	Frequency	Ratio*
All groups	**238,647**	**4,610**	**0.019**	**1:52**
Arab	9,058	152	0.017	1:60
Asian	119,718	2,492	0.021	1:48
Asian Indian	1,465	20	0.014	1:73
Black (Sub-Saharan ancestry)	8,012	80	0.010	1:100
Caucasian	31,549	680	0.022	1:46
Hispanic	9,649	127	0.013	1:76
Jewish	59,196	1,059	0.018	1:56

* Calculated by HIQA evaluation team.
Source: Verhaart et al.[21]

3.2 Incidence of SMA

3.2.1 Estimates of Irish incidence

A dataset of children diagnosed with SMA in Ireland was provided by CHI at Temple Street; this indicates that from 2018 to 2022, 17 children were born and subsequently diagnosed with SMA.[82] Given the centralised nature of care since the advent of new treatments, these cases are considered to represent a complete dataset for paediatric onset SMA in children who were both born and diagnosed during this time period. However, some patients born during this period have yet to present to the centre as they have not developed symptoms or received a diagnosis to date. Therefore, these cases only represent a minimum incidence. In these five years, there were 293,066 registered births in Ireland, therefore suggesting a minimum incidence of SMA of 1 in 17,239 births.

To account for type III cases who may develop symptoms at any point from 18 months to up to 18 years of age, an analysis of cases diagnosed from 2018 to 2022 (as opposed to cases born from 2018 to 2022) was also conducted using further data from CHI at Temple Street. This analysis includes cases diagnosed during this period who may or may not have been born during this period. These data showed that there were 20 paediatric cases diagnosed from 2018 to 2022. Taking the registered births from 2018 to 2022 as a proxy for birth rates across the time in which these cases may have been born, this reflects an incidence of type I to III SMA diagnosis of 1 in 14,653 births.

Summary data from the Department of Molecular Genetics based at CHI at Crumlin were used to confirm the completeness of the Temple Street estimates.[82, 84] While the number of SMA cases was not always consistent between centres, the variation was explained by changes in testing patterns related to the HSE cyber-attack.[85, 86]

The incidence estimates above do not account for cases diagnosed as adults who represent probable type IV SMA during this timeframe. A small number of adult cases ($n < 5$) received a genetic diagnosis of SMA based on samples tested at CHI at Crumlin. Including these adult cases with the paediatric cases results in an incidence estimate for SMA diagnosis of 1 in 12,211 between 2018 and 2022. However, as there is no central register of all SMA cases in Ireland it is possible that some adult patients may have had their sample transferred to an international centre for testing. Therefore, this incidence estimate may be an underestimate.

These incidence estimates are in line with what would be expected relative to the international data outlined below. However, given the natural variation expected with rare diseases, coupled with the relatively short five year time horizon for which there is considered to be suitable data on patients diagnosed with SMA, no firm

conclusions regarding the similarity of the Irish population estimates to international norms can be drawn. Across the five year period (2018 to 2022), the number of cases born and diagnosed with SMA varied from three to four cases per year, and the number of paediatric patients diagnosed varied from one to seven cases per year.

3.2.2 International estimates of incidence

A 2017 review of the incidence of SMA internationally found that, on average across the included studies, the incidence was approximately 8 per 100,000 live births, or 1 in 12,500 live births.[21] The range across studies was five to 24 per 100,000 (or 1 in 20,000 to 1 in 4,166), likely reflecting geographical differences (for example, healthcare access or higher rates of consanguinity). The authors note that the majority of studies were conducted in small populations and prior to the time at which the *SMN1* gene was identified as causative (1995). As these studies are therefore based on clinical rather than genetic diagnosis, there is the potential for misdiagnoses, which may under or overestimate the true incidence.

A 2017 study, led by the same author as the review above, surveyed genetic laboratories across Europe with the aim of obtaining contemporary estimates of SMA incidence.[87] Survey responses were received from 122 laboratories across 27 countries. Collectively, of 18 country responses with sufficient information, 4,560 patients were identified as having been genetically diagnosed with SMA from 2011 to 2015. The median incidence of SMA was 11.9 per 100,000 (ranging from 6.3 to 25.5 per 100,000) or 1 in 8,403 live births (ranging from 1 in 15,873 to 1 in 3,922). It is important to note that the responses to the survey indicate the laboratory location and not necessarily the residency of the patient. Therefore, some of the variability in incidence rates may be related to cross-border testing and or diagnosis occurring in neighbouring countries. Additionally, the survey response rate was not complete for all countries; however, a concerted effort was made to include all main testing laboratories.

The observed incidence of SMA from population-based screening programmes is outlined in detail in chapter 4 (clinical effectiveness) but briefly, this ranged from 1 in 19,000 to 1 in 6,059 (midpoint 1 in 13,500) across 13 studies. To note, this incidence reflects SMA caused by homozygous deletions in *SMN1* only, given the nature of the screening target (that is, these figures do not capture cases resulting from compound heterozygous variants).

It should be highlighted that, in the absence of screening, the incidence estimates for type IV SMA cases in particular may be limited due to these being adult onset and the mildest form (see section 2.2.2). It is plausible that such cases may be underdiagnosed or misdiagnosed. However, there is no means to reliably estimate

the extent to which this occurs. Similarly, a 2008 study of asymptomatic individuals with homozygous *SMN1* disruption noted that identification of asymptomatic SMA is rare.[88] The study genetically assessed 490 clinically healthy family members of SMA cases, and 300 healthy controls. Among the healthy family members, a bi-allelic deletion in the *SMN1* gene was found in three individuals, aged 25 years, 47 years, and 53 years at the time of the study, while no such deletions were identified in controls. However, in two of the three individuals in whom bi-allelic changes were identified, neurogenic changes on electromyography (EMG) were also noted (with EMG not being assessed in the third). Therefore, while these individuals were clinically asymptomatic, neurological changes were in fact present. The authors highlight the difficulty of interpreting these changes given the fact that mild neurogenic changes were also observed in a healthy sibling of an SMA patient who is a heterozygous deletion carrier, with only one copy of *SMN1*. Up to the time of publishing, the authors noted that they were aware of 23 similar cases with asymptomatic SMA documented in the literature, across 19 families. The authors caution that the emergence of clinical symptoms in these cases in the future cannot be excluded given the late onset form of the disease.

3.2.3 Subtype incidence

The 2017 review described above, the most recent review on this topic identified, further sought to estimate the incidence of each SMA subtype.[21] The authors presented the incidence for types I, II, and III for each study individually. As with the estimate of SMA incidence overall, there was variation in incidence noted across studies.

Meta-analysis of incidence of SMA by subtype based on Verhaart et al. (2017)

In order to provide synthesised estimates, and to inform the budget impact analysis (chapter 6), a meta-analysis of the incidence of each subtype was undertaken using data presented for individual studies in the Verhaart et al. 2017 review.[21] This was performed by the HIQA evaluation team using a random-effects GLMM approach. Data for general populations were included in the analysis, while specific cohorts with known higher incidence rates (for example, geographically isolated communities) were excluded. The estimated incidence calculated per subtype using this approach was:

- type I: 5.93 per 100,000 births (95% prediction interval (PI): 2.96 to 10.66)
- type II: 2.71 per 100,000 births (95% PI: 0.91 to 6.38)
- type III: 2.45 per 100,000 births (95% PI: 0.62 to 6.64)

Prediction intervals are presented rather than confidence intervals. This is because the inputs into the analysis represent incidence estimates derived from different

regions or countries. For the purposes of this HTA, we are interested in predicting the uncertainty surrounding the future incidence of SMA in an individual study or country (Ireland), which is represented by the prediction interval, rather the uncertainty in the average worldwide estimate (as estimated by the confidence interval).

Estimates of subtypes 0, IIIa, IIIb, and IV

No reliable estimates of the incidence of type 0 or type IV SMA were identified from the literature to inform this HTA. As noted, the incidence of these cases is challenging to reliably estimate given the potential for early mortality (in the case of type 0) and underdiagnoses or underreporting (in type IV). Studies describing SMA prevalence or the relative prevalence of different SMA types in European countries have outlined that type 0 encompasses 0.31% to 2.79% of all SMA cases, with type IV encompassing 0.63% to 2.09%.[89-91] However, the percentage of type I SMA cases in these studies (range 20% to 27%) is lower than expected, given the incidence of the disease; this is likely due to the mortality associated with this subtype and reflects prevalence-based estimates. Therefore, plausibly, given such estimates are impacted by the potential for mortality in type I SMA cases, the true number of type 0 and type IV cases is likely to be lower (that is, if there were no mortality in type I then the proportions for type 0 and type IV would be lower). However, again, this may be offset by under-diagnosis or underreporting of these cases overall. As type 0 SMA will not influence this HTA (that is, this cohort are identified at birth and the standard of care will remain the same), the incidence for this subtype was not estimated. For the purposes of this HTA, type IV patients were estimated as representing 1% of cases, generating an incidence of 0.11 per 100,000 births (95% PI: 0.01 to 0.35). This estimate was taken from the prevalence range reported above (0.63% to 2.09%) considering such cases are likely to have a normal life expectancy, and under the assumption that the true proportion of patients who have type IV SMA is at the lower end of the range.

Based on the incidence estimates above, the incidence of type I to IV SMA is estimated at 11.2 per 100,000 births (95% PI 4.1 to 22.8) or 1 in 8,932 (1 in 24,423 to 1 in 4,394). This is equivalent to an average of 6.5 cases (95% PI: 2.4 to 13.2) a year in Ireland based on approximately 58,000 births.

Proportionally, considering the meta-analysis and the above estimates, the breakdown of SMA cases by subtype estimated within this HTA was:

- type I: 55.3% (95% PI: 45.3 to 68.4)
- type II: 23.3% (95% PI: 19.3 to 25.4)
- type III: 20.4% (95% PI: 12.2 to 26.5)
- type IV: 1.0% (95% PI: 0.1 to 2.8)

Considering type III SMA specifically, as is discussed in section 3.4.2, there is a broad spectrum of age at onset within this group (that is, 18 months to 18 years). While estimates of incidence were not identified within this HTA, six prevalence based studies were identified from a 2018 review paper which provided a proportional estimate of type IIIa (that is, onset from 18 months to three years) and type IIIb (that is, onset from three to 18 years).[22] The weighted proportions across studies were calculated by the HIQA evaluation team as 53.6% for type IIIa and 46.4% for type IIIb.

3.2.4 Concordance of type amongst siblings

Given the inheritance pattern of SMA, familial cases of multiple affected siblings exist. From a database of self-identified individuals with types I-IV SMA globally from 1996 to 2016, the Cure SMA project (a US based advocacy and funding body) examined the concordance of SMA types in 627 individuals representing 303 groups of siblings (285 with two siblings, 15 with three siblings, and three with four siblings).[92] The authors identified that 84.8% (n = 257) had concordant SMA subtypes and 15.2% (n = 46) had discordant SMA subtypes. Given that the database involved self-identification by patients and given limitations in the study design, it should be noted that this sample may not be representative. However, it represents the largest study of sibling concordance identified within this HTA.

3.3 Genotype-phenotype correlations

SMN2 copy number represents the main prognostic biomarker used in clinical practice for SMA,[2, 5, 17, 18] with the quantification of copy number used as a guide for treatment options in those with SMA who are presymptomatic.[2] In general, higher copy numbers of *SMN2* are associated with lower disease severity.[2, 17, 18, 22] However, while a correlation between *SMN2* copy number and clinical severity exists, it is not absolute and discordant cases do present.[2, 22]

Data from contexts where screening is already in place cannot inform the determination of how *SMN2* copy number corresponds to SMA subtype. This is because almost all patients identified with SMA through screening will be asymptomatic at diagnosis and, where treatment occurs prior to symptom onset, a clinical subtype (which reflects the natural history of the condition) cannot be assigned. As such, the correlation of genotype with subtype must be informed by historical data based on clinical presentation.

A 2018 study sought to determine *SMN2* copy number by SMA subtype in 625 Spanish SMA patients and further compiled international reports of *SMN2* copy number across SMA subtypes from 33 studies published from 1999 onwards.[22] The HIQA evaluation team identified three additional studies of relevance since the

publication of this dataset.[63, 89, 90] Collectively, from the 2018 paper, the international dataset, and the additional studies identified, data on *SMN2* copy number across SMA subtypes were available for 4,672 cases.

Meta-analysis of the proportion of SMA subtype within copy number

To indicate the likely clinical course for individuals with particular *SMN2* copy numbers, and to inform the budget impact analysis (chapter 6), a meta-analysis of the above studies relating to *SMN2* copy number (the 2018 review and the additional studies identified) was completed by the HIQA evaluation team using a random-effects GLMM approach.[93]

In terms of considering how copy number corresponds to SMA subtype, the key figures are outlined below. Based on historical data, which are derived from a non-screening context (that is, patients presenting clinically with types I to IV):

- Those with up to three copies of *SMN2* represented 85.0% (95% CI: 65.3% to 94.5%) of patients with SMA.
- Those with four copies of *SMN2* were estimated to represent 11.1% (95% CI: 4.3% to 19.9%) of the patients, while those with five or more copies represented 3.9% (95% CI: 0.0% to 22.8%).
- Among those with up to three *SMN2* copies, 99.8% (95% CI: 98.8% to 100%) are estimated to reflect types I to III SMA, while the remaining 0.2% (95% CI: 0.0% to 1.2%) are estimated to have type IV disease.
- Among those with four *SMN2* copies, 94.4% (95% CI: 82.8% to 99.2%) are estimated to reflect types I to III SMA, while the remaining 5.6% (95% CI: 0.8% to 17.2%) are estimated to have type IV disease.
- Among those with five or more copies of *SMN2*, the uncertainty is too large (confidence intervals ranging from 0% to 100%) to estimate the proportion falling into particular types; however, the direction of effect suggests that such individuals would have milder SMA.

Patients with up to three *SMN2* copies are considered as one group here for simplicity; this grouping reflects genotypes which are more likely to represent paediatric-onset phenotypes, and is also the grouping of patients for which immediate treatment of SMA was suggested in the 'possible Irish treatment pathway' identified (see chapter 2, description of technology).

It is important to note that if screening were to identify cases that previously would have gone undiagnosed due to their mild clinical course, the proportion of those with

severe disease would decrease as a proportion of the total SMA cases identified, while, correspondingly, the proportion of those with mild disease would increase.

The meta-analysis results are presented in Table 3.2 in the inverse format of the proportion of each copy number within each subtype.

There are a number of limitations to the data which informed this meta-analysis. Multiple studies were from single countries, resulting in the potential for duplicate reporting of cases. Also, some studies only looked at certain subtypes, which may impact on the representativeness of the samples included. Additionally, there is the potential for discrepancies in subtype clinical definitions, and some studies grouped higher copy numbers (for example, into 'four or more'). To note, no cases with six *SMN2* copies were identified among types I and II, and no cases with one *SMN2* copy number were identified among types III and IV.

Table 3.2 Meta-analysis results of proportional breakdown of *SMN2* copy numbers within each SMA subtype

	***SMN2* copy number Mean percentage (95% CI)**			
	type I	**type II**	**type III**	**type IV**
1 *SMN2* copy	7.5 (0.7 to 26.3)	0.9 (0.0 to 7.4)	-	-
2 *SMN2* copies	69.1 (33.9 to 94.4)	13.2 (0.5 to 45.9)	6.9 (0.3 to 29.8)	12.3 (0.0 to 53.5)
3 *SMN2* copies	20.3 (0.9 to 54.5)	73.4 (31.3 to 97.2)	46.3 (18.9 to 74.4)	7.3 (1.6 to 18.9)
4 *SMN2* copies	0.5 (0.0 to 2.3)	5.6 (0.1 to 28.4)	43.5 (16.2 to 72.6)	63.0 (27.5 to 93.5)
5 *SMN2* copies	2.6 (0.0 to 37.5)	6.9 (0.0 to 54.0)	2.5 (0.0 to 19.5)	14.2 (0.0 to 55.9)
6 *SMN2* copies	-	-	0.8 (0.0 to 6.4)	3.2 (0.2 to 13.3)

Key: *SMN2 - survival of motor neuron 2.*
This analysis considers each subtype separately and hence it is to be read as distinct columns which sum to 100.

SMN2 copy number by subtype from the Irish cohort

For the Irish data, copy number breakdown for adult cases was unavailable and therefore the likely clinical course based on *SMN2* copy number could not be reliably estimated.

From the dataset provided by CHI at Temple Street, copy number by subtype was available for 52 cases born from 2001 onwards.[82] Within each paediatric subtype, the proportional breakdown of copy number was as follows:

- type I (n = 16): two (n = 15, 93.8%) or three (n = 1, 6.2%) *SMN2* copies
- type II (n = 29): three copies (n = 29, 100%)
- type III (n = 7): three (n = 6, 85.7%) or four (n = 1, 14.3%) copies

Of paediatric cases presenting clinically, only one patient out of 52 cases had more than three copies of *SMN2.* Therefore, as expected, cases presenting clinically with paediatric onset disease have generally had lower *SMN2* copy numbers. However, these data are based on a very small number of patients who specifically presented for diagnosis in the paediatric setting. The potential for an undiagnosed population cannot be eliminated.

3.3.1 Other biomarkers

Additional biomarkers are noted in the literature, including molecular-based biomarkers (for example, *SMN2* variants c.859G > C and c.863G > T) and electrophysiological and imaging-based biomarkers (for example, compound muscle action potential).[94] However, most are not routinely used in clinical practice.[26]

3.4 Clinical presentation

SMA is characterised by muscle atrophy and weakness. This weakness is typically symmetrical, proximal greater than distal, and progressive in nature.[2, 5] In more severe forms of SMA the bulbar nerve can be impacted. This affects feeding and leads to a failure to thrive. The intercostal nerves can further be impacted resulting in respiratory difficulty which often presents as a bell-shaped chest with paradoxical breathing.[5] Potential clinical findings by SMA subtype are outlined in Table 3.3.[1, 5]

Table 3.3 Potential clinical findings by SMA subtype

SMA type	Potential clinical findings
type 0	▪ Severely reduced muscle tone ▪ Severe weakness ▪ Absence of reflexes ▪ Respiratory failure at birth ▪ Facial palsy ▪ Reduced foetal movements ▪ Heart defects ▪ Congenital contractures
type I	▪ Loss of head control ▪ Joint contractures ▪ Normal or minimal facial weakness ▪ Variable suck/ swallow difficulties ▪ Scoliosis ▪ Respiratory impairment
type II	▪ Developmental delay ▪ Reduced or absent deep tendon reflexes ▪ Proximal muscle weakness ▪ Postural tremor of fingers ▪ Scoliosis ▪ Contractures ▪ Respiratory impairment
type III	▪ Proximal muscle weakness (difficulty with stairs, running) ▪ Loss of motor skills ▪ Fatigue ▪ Postural tremor of fingers ▪ Loss of lower limb reflexes
type IV	▪ Fatigue ▪ Proximal muscle weakness

Source: Prior and Leech,[5] Mercuri et al.[1]

3.4.1 First clinical symptoms

As noted, type 0 SMA is associated with symptoms at birth. A 2016 French registry study of SMA cases from 1999 to 2014 identified 16 type 0 cases.[95] All were considered to have profound hypotonia at birth with an absence of deep tendon reflexes, and the majority had joint contractures. All patients were further noted to have significant respiratory impairment at birth with most cases requiring mechanical ventilation within the first minutes or hours of life.

A 2020 Italian study of type I-III SMA noted that for the majority of cases symptoms were first recognised by parents regardless of type.[96] The first symptoms by SMA subtype reported by the study are outlined in Table 3.4.

Table 3.4 First clinical symptoms identified in SMA types I-III

SMA type	First symptoms (%)
Type I (n = 191)	▪ General hypotonia (59.2%) ▪ Developmental delay – head control (17.3%) ▪ Absence of antigravity movement (7.9%) ▪ Respiratory distress (7.9%) ▪ Developmental regression (3.7%) ▪ Feeding issues (3.1%) ▪ Absence of deep tendon reflexes (1.1%)
Type II (n = 210)	▪ Not standing (39.5%) ▪ Developmental delay – sitting position (20.5%) ▪ Hypotonia – lower limbs (18.1%) ▪ Not crawling (1.9%) ▪ Failure to thrive (0.5%) ▪ Respiratory infections (0.5%)
Type III (n = 79)	▪ Unsteady gait (28.8%) ▪ Falls (22.5%) ▪ Difficult in rising from floor (12.5%) ▪ Difficulty in climbing stairs (11.3%) ▪ Developmental delay (5.0%) ▪ Developmental regression (3.8%) ▪ Difficulty running (3.8%) ▪ Clumsy movements (3.8%) ▪ Muscle weakness (2.5%) ▪ Toe walking (2.5%) ▪ Accidental finding (2.5%) ▪ Tremor (1.3%)

Source: Pera et al.[96]

For type IV SMA, a 2020 retrospective review of 227 Brazilian patients with SMA found that, of 20 patients identified, the majority first presented with proximal lower limb weakness (75%), followed by cramp-fasciculation (20%), and a single case (5%) of asymptomatic elevated creatine kinase.[97] The suspected pathologies prompting referral were limb girdle muscular dystrophy in 60% of cases followed by amyotrophic lateral sclerosis (20%), inflammatory myopathy (10%), and chronic inflammatory demyelinating polyradiculoneuropathy (10%).

3.4.2 Age at symptom onset

The classification of SMA subtype, in the absence of screening, is in part based on age at clinical onset. The general categorisation of SMA subtypes on this basis is outlined in Table 3.5.[2, 3, 5]

Table 3.5 Diagnostic classification of SMA based on age at clinical onset

SMA subtype		Age at onset
Type 0		Prenatal
Type I		< 6 months
Type II		6 - 18 months
Type III	a	18 months - 3 years
	b	3 years - adulthood
Type IV		Adulthood

Key: SMA – spinal muscular atrophy.
Source: Prior and Leech,[5] Wirth et al.[2], Keinath et al.[3]

As outlined previously, type 0 SMA is associated with a prenatal onset and therefore an infant will have symptoms consistent with the disease at birth.[2, 95]

From the Irish context, of 25 paediatric cases with data on age at symptom onset provided by CHI at Temple Street, the median age for type I was four months (range 1.3 to 4.0 months), type II was 12 months (range 7.9 to 18 months), and type III was 114 months (range 24 to 144 months).[82] These cases all presented between 2015 and 2022. A 2015 systematic review of age at symptom onset for SMA type I, II, and III identified 21 studies from 2000 to 2014. The weighted mean age of symptom onset across studies was:[98]

- type I SMA: 2.5 months (standard deviation (SD) = 0.6, range 1 to 11 months)
- type II SMA: 8.3 months (SD = 1.6, range 2 to 18 months)
- type III SMA: 39.0 months (SD = 32.6, range 5 to 192 months).

A 2020 Italian study of 480 children diagnosed with SMA in five neuromuscular centres from 1996 to 2019 provides similar results in terms of the mean age of onset:[96]

- type I SMA: 2.8 months (SD =2.0, range 0 to 10 months)
- type II SMA: 10.4 months (SD = 4.0, range 3 to 24 months)
- type III SMA: 31.8months (SD = 37.9, range 9 months to 15 years)
    - type IIIa: 18.1 months
    - type IIIb: 84.7 months.

For type IV SMA, a 2020 retrospective review of 227 Brazilian patients with SMA identified 20 patients with this subtype. The median reported age of onset was 31.4

years (range 21 to 51 years).[97] Similarly, a 2018 cross-sectional study of patients with SMA from The Netherlands reported a median age of onset of 38 years (range 31 to 44 years) for six patients with this subtype.[99]

3.4.3 Age at diagnosis

From the Irish context, of 25 paediatric cases with data on age at diagnosis provided by CHI at Temple Street, the median age for type I was six months (range 0 to 7.9 months), type II was 19 months (range 12 to 24 months), and type III was 144 months (range 42 to 192 months).[82] These cases all presented between 2015 and 2022.

The same 2015 systematic review outlined above estimated the weighted mean age at diagnosis for type I, II and III SMA patients:[98]

- type I SMA: 6.3 months (SD = 2.2, range 0.6 to 9 months)
- type II SMA: 20.7 months (SD = 2.6, range 1.2 to 72 months)
- type III SMA: 50.3 months (SD = 12.9, range 3 to 82.8 months).

Again the 2020 Italian paper outlines similar results:[96]

- type I SMA: 4.7 months (SD = 2.8, range 10 days to 13.2 months)
- type II SMA: 15.6 months (SD = 5.9, range 5 to 53 months)
- type III SMA: 52.1 months (SD = 48.1, range 10 to 216 months)
    - type IIIa: 32.6 months
    - type IIIb: 117.8 months.

3.4.4 Delay between symptom onset and diagnosis

It is important to note that the 2015 systematic review outlined above considers different patient cohorts for age at symptom onset and age at diagnosis so the two weighted means cannot be directly compared. However, a limited number of studies provided both estimates to inform estimation of diagnostic delay:[98]

- type I SMA: 3.6 months (SD = 1.9, range 1.0 to 5.9 months, three studies)
- type II SMA: 14.3 months (one Chinese study)
- type III SMA: 43.6 months (one Chinese study).

For the 2020 Italian study shorter intervals are outlined:[96]

- type I SMA: 1.9 months (SD =1.8; range 0 to 10.3 months)
- type II SMA: 5.3 months (SD = 4.7; range 0 to 35 months)
- type III SMA: 16.8 months (SD = 18.7; range 0 to 102 months)
    - Diagnostic delay was noted to be shorter for type IIIa than type IIIb.

While not providing age at diagnosis for type IV cases, the 2020 Brazilian study outlines a mean delay of 12.4 years (+/- 7.3 years) from symptom onset.[97]

Collectively across the studies identified within this HTA, the interval from symptom onset to diagnosis appears to increase across SMA subtypes with type I associated with the shortest diagnostic delay and type IV with the longest, likely reflective of the clinical severity of each subtype making recognition of symptoms more challenging as severity reduces.

3.5 Natural history and burden of disease

3.5.1 Natural history by SMA subtype

Given the heterogeneity of disease severity, the natural history of SMA is outlined by subtype below. To note, this encompasses the typical progression of the condition in the absence of significant therapeutic intervention. It should be highlighted that many of the studies outlined below were associated with potential conflicts of interest including industry-based employment, funding, consultancy and or advisory fees.

Type 0 SMA

There is a scarcity of literature describing the natural history of type 0 SMA. For the most part this group is described as having limited life expectancy due to prenatal onset and a rapid deterioration of clinical state.[2, 5, 95] Hence, the type of treatment for these patients is typically restricted to supportive and palliative care. One study was identified which described a cohort of 16 type 0 SMA cases from a French registry.[95] As outlined in section 1.4.1, this cohort had significant musculoskeletal and respiratory impairment at birth with the latter meaning that all required mechanical ventilation. All 16 infants died within approximately one month with the median age at death being 15 days (range six to 33 days).

Type I SMA

Four studies were identified which provided detailed descriptions of the natural history of type I SMA. The characteristics of these studies are outlined in Table 3.6.

Table 3.6 Type I SMA natural history study characteristics

Study	Location	Population	Outcomes	Follow-up
PNCR Network for SMA 2014[100]	Three US sites	34 type I SMA cases *SMN2 copy number:** ▪ Two copies (n = 23) ▪ Three copies (n = 9)	▪ Mortality ▪ Requiring at least 16 hours per day of non-invasive ventilation support for at least 14 days ▪ CHOP-INTEND scores	At least 12 months
NeuroNEXT network 2017[101]	Multicentre US study	26 type I SMA cases *SMN2 copy number:*^ ▪ Two copies (n = 16) ▪ Three copies (n = 5) ▪ Four copies (n =1) Healthy controls: n = 27	▪ Mortality ▪ Intubation ▪ CHOP-INTEND or AIMS scores depending on baseline function ▪ CMAP	24 months
ANCHOVY study 2022[102]	International chart review study across nine countries	60 type I SMA cases *SMN2 copy number:* ▪ Two copies (n = 30) ▪ Unknown (n = 30)	▪ Event free survival (death or permanent ventilation) ▪ HINE-2 scores ▪ Initiation of respiratory support ▪ Swallowing and feeding support ▪ Growth measurements	Up to 24 months
Oskoui et al 2007[103]	International Spinal Muscular Atrophy Patient Registry	143 type I SMA cases	▪ Survival of patients born in 1995 to 2006 (n = 78) compared with patients born in 1980 to 1994 (n = 65)	Mean follow-up of 49.9 months

Key: AIMS - Abnormal Involuntary Movement Scale; CHOP-INTEND - Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; CMAP - compound muscle action potential; HINE - Hammersmith Infant Neurological Examination; NeuroNEXT - National Network for Excellence in Neuroscience Clinical Trials; PNCR - Paediatric Neuromuscular Clinical Research; SMA – spinal muscular atrophy; *SMN2 - survival of motor neuron 2*.
* available for 32 children, ^ available for 22 children, +available for 15 children.

The 2014 Paediatric Neuromuscular Clinical Research (PNCR) study included a mixture of type I cases enrolled within three months of diagnosis and after three months of diagnosis, and the group was further subdivided into those with symptom onset before three months of age and after three months of age.[100] Nine (26.5%) out of 34 participants died during the study period with the cause of death being acute pulmonary infection (n = 6), airway obstruction (n = 2), and bradycardic arrest (n = 1). The median age at reaching the combined endpoint of mortality or requiring 16 hours of non-invasive ventilation per day was 13.5 months (IQR 8.1 to 22.0). The age distribution at reaching the combined endpoint was similar for subjects with SMA type I who had symptom onset before three months and after three months of age. The mean rate of decline in Children's Hospital Of Philadelphia Infant Test Of Neuromuscular Disorders (CHOP-INTEND) scores (a scale assessing ability to perform certain movements; see chapter 2: description of technology) was 1.27 points per year (95% confidence interval (CI) 0.21 to 2.33) (of a total possible CHOP-INTEND score of 64). Children with two *SMN2* copies were noted to have higher morbidity and mortality than those with three *SMN2* copies.

Twelve (46.2%) of 26 type I patients died over the course of the 2017 NeuroNEXT study while seven more withdrew from the study.[101] *SMN2* copy number was inversely associated with risk of death or permanent invasive ventilator support: there was an eight times higher risk of these outcomes in those with two *SMN2* copies or an unknown copy number compared with those with more than two copies of *SMN2* (hazard ratio (HR) = 8.13, 95% CI 1.1 to 63.0). The median survival time for SMA infants with two *SMN2* copies was eight months (95% CI 6 to 17). The median survival time for the SMA infants with more than two SMN2 copies was not reached, with 85% alive at 24-months follow-up.

The ANCHOVY study was a retrospective chart review study across nine countries which sought to describe the natural history of type I SMA to provide comparisons for ongoing trials of the risdiplam drug.[102] Thirty cases had two *SMN2* copies with copy number unknown for a further 30. The median age of reaching the primary endpoint of death or permanent ventilation was 7.3 months (interquartile range (IQR) 5.9 to 10.5), while the median age at permanent ventilation was 12.7 months (IQR 6.9 to 16.4) and at death was 41.2 months. The median age at initiation of respiratory support was 8.8 months (IQR 6.8 to 13.9) and for initiation of feeding support was 6.9 months (IQR 5.3 to 14.7). With a large amount of missing data points, data on motor development were obtained from nine participants at 12 months of follow up, none of whom were able to sit without support or none of whom achieved any further motor milestones.

Given the increasing availability of proactive clinical care for patients with SMA (for example, non-invasive ventilation), a 2007 US study sought to explore, using registry

data, whether there had been a change in survival over time in patients diagnosed with type I SMA between 1980 and 2006.[103] Survival of patients born in the period of 1995 to 2006 (n = 78) was compared with patients born from 1980 to 1994 (n = 65). Patients born in the later period had significantly increased survival compared with those born in the earlier period (HR for risk of death = 0.3, 95% CI 0.2 to 0.5). Factors influencing this finding included the availability of ventilation support for more than 16 hours per day, airway clearance devices, and gastrostomy tube feeding.

Type II and III SMA

Studies of type II and III SMA were largely not disaggregated within the available literature. As such, these groups are presented collectively here with clear differences highlighted wherever possible.

A 1997 study of SMA cases in Germany and Poland estimated the survival probability of type II SMA to be 98.5% at five years, reducing to 68.5% at 25 years.[104] The same study outlined that survival in type III cases was not significantly different to normal life expectancy; however, precise estimates were not provided by the authors.

The 2020 NatHis-SMA study was conducted across nine centres in Belgium, France, and Germany. In this study, 53 type II (non-sitters = 19, sitters = 34) and 28 type III (non-ambulant = 9, ambulant = 19) cases were assessed over a 24 month period for changes in motor and pulmonary function, among other clinical data.[105] Motor function, as measured by the 32-item Motor Function Measure assessment, declined significantly over 24 months but not over 12 months in the total population. Of note, post-hoc analyses indicated that the change was only significant in non-sitters with type II SMA; declines in other groups did not reach statistical significance. Upper limb strength decreased significantly over 12 and 24 months across the population. Pulmonary function, measured by forced vital capacity, declined significantly over 12 months, but not 24 months.

A 2012 prospective observational cohort study reported findings of changes in clinical outcomes up to 48 months in 79 cases of type II (n = 41) and III (n = 38) SMA across clinical PNCR network sites.[106] Outcomes assessed included motor function, pulmonary function, quality of life, and muscle strength. Across the study cohort, motor and pulmonary function were reported to decline over time in a non-linear manner, particularly at time points beyond 12 months of follow-up. In terms of motor milestones, two participants with type II SMA (5%) and one participant with type III SMA (3%) lost the ability to sit during the study, while five participants with type III SMA (13%) lost the ability to walk. No significant declines were observed in quality of life, muscle strength, or electrophysiological measures.

Specifically with regards to ambulation in type III cases, a 2021 study of Polish registry data, which included 393 cases with this subtype, outlined that 44% (n = 172) had maintained the ability to walk with the mean age of loss of this function being 14 years (SD = 11).[107] The probability of preserved ambulation for 293 patients was presented and is outlined in Table 3.7 for various time points of disease duration (the attrition was not explained by study authors but may relate to complete time points). As shown, the reduction is more pronounced in those with type IIIa (onset before three years of age) as opposed to those with type IIIb (onset after three years of age). The authors further highlight that those with four *SMN2* copies were more likely to maintain ambulation than those with three *SMN2* copies.

Table 3.7. Probability of being ambulatory in type III SMA

	Probability of being ambulatory at different time points of disease duration			
	10 years	20 years	30 years	40 years
Type III (n = 293)	80%	68%	61%	60%
Type IIIa (n = 159)	58%	37%	33%	31%
Type IIIb (n = 134)	89%	78%	69%	66%

Source: Lusakowska et al.[107]

Type IV SMA

Limited data were identified in the literature for the natural history of type IV SMA. A 2008 Dutch study of late onset SMA included 12 patients with type IIIb (n = 7, inferred from participants aged under 18 years at onset) or type IV (n = 5, inferred from participants aged over 18 years at onset) with a follow-up ranging from 19 to 36 months.[108] At follow-up, no significant change in muscle strength, functional impairment, or respiratory function was noted across the study cohort. To note, at recruitment the median disease duration was eight years (range 0 to 25).

The development of scoliosis

A 2019 Dutch study using registry data included 283 patients with SMA types I to IV ranging in age from 0 to 82.2 years.[109] Collectively across the study population, 170 patients (60.1%) had scoliosis, and 95 (33.6%) underwent scoliosis surgery. The lifetime probability of requiring scoliosis surgery was calculated by the study authors and differed significantly across SMA types:

- type Ic (a subset of type I) (n = 29, onset age 3-6 months): 77% (95% CI 26.2 to 92.9)
- type II (n = 120, onset age 6-18 months): 84% (95% CI 72.0 to 90.6)

- type IIIa (n = 53, onset age 18 months – three years): 40% (95% CI 20.7 to 54.4)
- type IIIb (n = 44, onset age older than three years): 2%, (95% CI 0.0 to 6.6)
- type IV (n = 6, onset in adulthood): 0 cases.

Specifically in type III SMA, the need for scoliosis surgery was associated with age at loss of ambulation.

The development of scoliosis has significant consequences for the functional ability of those with SMA and for their treatment options, particularly in the context of the intrathecally delivered drug nusinersen. Progressive curvature of the spine can result in a required cessation of this treatment. The 2018 diagnostic guidelines for SMA note the development of scoliosis in type I and type II non-ambulatory patients with SMA to be as high as 60-90% with initial presentation in early childhood.[1]

3.5.2 Quality of life

Children with SMA

A 2020 cross-sectional study of 86 children with SMA across the UK, France, and Germany sought to estimate health related quality of life (HR-QoL).[110] The population included type I (26.7%), type II (52.3%), and type III (20.9%) SMA patients with a mean age of less than 10 years across type and location. HR-QoL was measured using a proxy version of the EuroQol 5-dimensions with 3-levels (EQ-5D-3L) with standardised reference values of 0 for death and 1 for perfect health, although negative values are also possible. Additionally, a visual analogue scale (VAS) was used where participants were asked to rate their overall health on the day of data collection from 0 to 100. The date of data collection (2015) predates the use of disease-modifying treatments in this population and hence the results reflect children treated with supportive therapy only. Results indicated that children from the French and UK cohorts had a lower HR-QoL, with a utility score of 0.12 and 0.17 respectively, compared to that of the German cohort with 0.53. The authors note that the differences in results between the locations is not explained by age or disease progression. On the VAS measure, mean scores were higher across the three locations with 75.44 (SD = 19.36), 59.15 (SD = 29.84), 69.76 (SD = 13.42).

A 2017 Spanish study used similar measures to estimate QoL in 81 patients with type I (10%), type II (74%), and type III (16%) SMA who had a mean age of 7.2 years (SD = 5.5) and again were assessed prior to availability of disease-modifying treatments.[111] The mean HR-QoL time-trade off social tariff score was 0.16 (SD = 0.44), with the VAS measure being 54.09 (SD = 26.30).

It should be highlighted that the instruments used in these studies have not been validated in child responders.

Caregivers

Both studies described above further estimated QoL in the caregivers of children with SMA, with a five level EQ-5D used in place of the three level measure.[110, 111] In the first study across the UK, France, and Germany, mean caregiver QoL scores for 56 caregivers were 0.85 (SD = 0.16), 0.40 (SD = 0.47), and 0.80 (SD = 0.30), respectively, with VAS measures being 80.36 (SD = 17.01), 62.12 (SD = 33.41), and 71.92 (SD = 14.20).[110] In Spain the mean QoL score was 0.48 (SD = 0.45) with a VAS score of 69.1 (SD = 22.0).[111]

Each study further estimated the mean estimated daily caregiving time in hours with 12.50 (SD = 5.96) in the UK, 9.31 (SD = 8.44) in France, 10.65 (SD = 5.45) in Germany, and 8.22 in Spain.[110, 111] The Zarit interview was administered as a measure of burden experienced by carers with the measure ranging from 0 to 88, scores under 21 representing little or no burden and scores above 61 representing severe burden. Mean scores were 26.63 (13.39) in the UK, 40.37 (SD = 16.10) in France, 21.33 (SD = 18.33) in Germany, and 34.53 (SD = 13.41) in Spain.[110, 111]

3.5.3 Healthcare utilisation in the absence of disease-modifying treatments

The literature identified for healthcare utilisation primarily reflects estimates in the period before disease-modifying treatments were available (that is, they do not reflect the current standard of care for patients with SMA).[110, 112] Collectively, in this context, the annual direct medical costs and resource use were reported to be highest for those with type I SMA, with an incremental reduction across type II and type III SMA. Limited data were available for those with type IV SMA.[112, 113] However, given the limited life expectancy of type I SMA patients in the absence of disease-modifying treatments, patients with types II and III SMA would incur higher costs over a lifetime compared with patients with type I SMA.[112]

Estimated resource use varies considerably between countries, likely attributable to differences in practice and healthcare system structuring.[112] Available evidence suggests that direct care costs are considerably lower in Europe than in the US.[114] However, estimates of resource use and associated costs in the European context are limited. In Spain, results of a retrospective multicentre analysis (n = 705) set during the period 1997 to 2015 indicate that approximately 58.2% of healthcare utilisation at a hospital level was attributable to scheduled appointments, with the remainder consisting of emergency admissions (41.7%).[115] The average duration of hospitalisation was 10.5 days, with 11.4% of patients readmitted within 30 days of

discharge.[115] Healthcare utilisation was not available by SMA type due to limitations of the database.

Only one study was identified that described the relationship between healthcare utilisation and SMA type. A US-based retrospective cohort study used age at diagnosis to categorise patients into infantile (n = 23), childhood (n = 22), or late onset (n = 296) cohorts.[116] Pulmonary services and nutritional support were most frequently used by patients in the infantile cohort.[116] All cohorts required orthopaedic care. As expected, requirements for inpatient hospitalisation decreased with increasing age at disease onset, with 91.3% of patients in the infantile onset cohort experiencing at least one inpatient hospitalisation during follow-up, compared with 50% and 37.2% of the childhood onset and late onset cohorts, respectively.[116]

3.5.4 Effectiveness of disease modifying treatment

An overview of disease-modifying treatments for SMA and the studies supporting EMA licensing are presented in chapter 5 (overview of treatments).

3.5.5 Healthcare utilisation in the context of disease-modifying treatments

A 2021 systematic review identified two studies reporting on the effect of disease-modifying treatments on direct medical costs and resource utilisation in patients with SMA; both studies centred on nusinersen.[112]

A retrospective review of 11 children with type I SMA who were treated with nusinersen in the UK reported that patients had a median of 11 (range 1 to 25) hospital admissions over the two-year study period.[117] This equated to a median of 84 (range 7 to 235) hospital days per child, or approximately 20% (range 2% to 72%) of their life.[117] Children had the greatest requirement for admission in the first six months following initiation of nusinersen, largely driven by the tendency for children to have a longer first admission (median 20 days per child (range 1 to 235)).[117] The most common reason for admission was lower respiratory tract infection.[117] A total of 762 high dependency unit days and 248 paediatric intensive care unit days were required by the 11 children over the two-year study period.[117] Importantly, children in this cohort were a median of 8.1 months (range 0 to 85.7) old at the time of the first dose of nusinersen, all children required long-term ventilator support, and of these, six children were ventilated prior to treatment initiation. Therefore, the reported healthcare utilisation in this cohort may not reflect resource requirements for patients with type I SMA for whom treatment is available at the time of diagnosis.

A second retrospective study based in the US grouped patients with SMA into four cohorts based on SMA type and treatment approach: type I SMA (n = 349), type I

SMA treated with nusinersen (n = 45), other SMA (types II, II and IV combined, n = 5,728), and other SMA treated with nusinersen (n = 404).[118] Over a period of eight to 10 months, irrespective of treatment, patients with type I SMA had a similar number of admissions (type I SMA: 1.9 admissions per patient per year; type I SMA treated with nusinersen: 1.7 admissions per person per year).[118] However, patients with type I SMA who initiated treatment with nusinersen had a lower average number of inpatient days per person per year relative to the overall population with type I SMA, suggestive of less severe disease (4.6 days versus 14.1 days, respectively).[118] In both groups, respiratory failure was the most frequent cause of medical visits, consistent with available evidence from the UK.[117, 118] Patients with type I SMA treated with nusinersen attended outpatient settings more frequently relative to patients with type I SMA managed with supportive care (24.8 days versus 10.5 days per person per year).[118] In the 'other SMA' and 'other SMA treated with nusinersen' cohorts, the average number of admissions per person per year was 0.4 and 0.5 respectively, accounting for 1.9 and 2.5 hospital days over the study period (9 to 14 months).[118]

No studies were identified that investigated the impact of early treatment initiation, either as a result of screening or family history, on resource utilisation.

3.6 Discussion

The purpose of this chapter was to outline the epidemiology associated with SMA, including the aetiology, incidence, clinical presentation, and burden of the disease, drawing on international and national data. SMA is a neuromuscular genetic condition caused by a lack of SMN protein.[2, 3, 5] Deficiency of SMN results in progressive axonal loss. Axons are crucial for muscle function with their loss leading to muscle wasting and weakness. Symptomatic patients with SMA are classified in terms of five subtypes, with a reducing level of severity and increasing age of onset moving from type 0 through to type IV.[2, 3, 5]

Estimates of the incidence of SMA were noted to vary internationally. While this is not unexpected in the context of a rare disease it should be noted that many of the studies predated the more advanced genetic testing methodologies presently available, were limited in terms of the completeness of data (for example, not including all potential laboratories testing in a country), or included estimates from populations known to be at a higher risk of SMA.[21, 87] Relevant data for estimating the incidence of cases in Ireland were available for a five year period between 2018 and 2022; analysis of these data resulted in an incidence estimate for SMA diagnosis of 1 in 12,211. While care of children with SMA in Ireland is centralised, care of adult patients is not. This means that some adult cases may not be included in these figures and the incidence could be underestimated. It should also be highlighted that

complete estimates of type IV SMA from the Irish perspective could not be obtained, with a similar limitation noted in the international literature. As outlined previously, this cohort are considered to represent the smallest proportion of all SMA cases but in the absence of reliable estimates of their incidence, coupled with the milder disease course seen in this subtype, their relative contribution to incidence cannot be reliably estimated.[2, 5] An important consideration is the impact of screening on the incidence of observed cases. For example, depending on the screening definition applied, a significant rise in incidence after the implementation of a screening programme may signal the detection of cases who were previously asymptomatic or so mildly impacted that they did not present clinically. As is detailed in chapter 4 (clinical effectiveness), screening programmes for SMA are in their relative infancy and hence reliable estimates of this impact are challenging to ascertain.

While not the focus of this HTA, the predominantly autosomal recessive nature of the condition means that the influence of carriers is an important consideration in the incidence of SMA. In Ireland, carrier testing is used in the event of a positive family history; that is, when a child is diagnosed, their parents, and in turn other adult relatives, are afforded the option of carrier testing. In addition, where a person is confirmed as a carrier (or as having a significant residual risk of being a carrier, after testing), their partner may be tested for carrier status to enable estimation of their risk of having an affected child.[26] This practice varies internationally with US recommendations advocating for carrier screening for those with and without a family history of SMA. A number of studies have used carrier frequency to estimate the incidence of SMA.[119, 120] As highlighted, this method may be considered as an alternative process to newborn bloodspot screening. However, it is not absolute and most commonly provides an estimated risk of carrier status in the general population (rather than definitive status), given the carrier genotypes that may evade such testing and the presence of *de novo* pathogenic variants independent of parent genotypes.[21] Where carrier genotypes that would evade population-based carrier screening are present in parents, the majority of affected children of such parents would be identified via the alternative approach of a newborn screening programme designed to detect homozygous absence of *SMN1* in newborns. Given the relatively high carrier frequency for SMA (1:52), studies have estimated expected incidence of the condition based on carrier frequency within individual countries.[121] However, these studies have been associated with an overestimation of the projected incidence relative to the observed incidence.[21, 87] For example, a US study projected an incidence of 16.7 per 100,000 live births from carrier frequency estimates with the observed incidence estimated as approximately 10 per 100,000 live births.[120, 122] A study of observed incidence in Poland estimated the incidence of SMA to be 10.7 per 100,000 live births which may be contrasted with a projected incidence from carrier frequency of 20.4 per 100,000 live births.[119] Hypothesised reasons for

these overestimations include:[21, 87] the availability of carrier testing and subsequent family planning, the availability of prenatal testing for higher risk pregnancies, in-utero or early neonatal mortality due to disease severity (particularly the lethality of an absence of *SMN1* in tandem with an absence of *SMN2,* the latter of which is estimated to be carried in 10 to 15% of the general population), the assumption of 100% penetrance, the potential for asymptomatic cases, and varying rates of consanguinity.

In terms of the relative proportion of SMA subtypes, prevalence-based studies are unable to appropriately estimate these values given the high mortality associated with type I before the availability of disease-modifying treatments. Restricting to incidence-based studies, as would be reflective of those identified through a newborn bloodspot screening programme, type I constitutes the largest proportion at approximately 50-60% with type II and III making up the vast remainder of cases, and type 0 and IV considered to represent a small minority (though again, given their nature, precise estimates are difficult to ascertain). As noted, type I further represents the most severe form for whom disease-modifying treatments are currently available with a reducing severity moving up the SMA subtypes. This reduction is noted in terms of physical impact, QoL, and caregiver burden. As is outlined further in chapter 5 (overview of treatments), the relatively recent emergence of disease-modifying treatments for this condition means that there are limited data on the longer-term impact of pre-symptomatic or early treatment on overall outcomes and associated burden. However, given the progressive and irreversible axonal loss associated with the condition, there is clear clinical plausibility to the potential benefits of earlier intervention.[123]

The introduction of newborn bloodspot screening for SMA would effectively remove clinical subtyping given the reliance of this process on the emergence of symptoms and age at onset. In this context, prognosis, and subsequent treatment decision-making, is reliant on the *SMN2* copy number of a case as a biomarker.[2, 17, 18] As highlighted, while a correlation exists between this biomarker and disease severity it is not absolute.[22] For example, type I SMA is most frequently associated with two *SMN2* copies, however, cases with four or more copies have been documented. Similarly, type IV SMA is typically associated with four or more copies, but cases with lower counts have been identified. On both ends of the spectrum this has implications for the treatment provided.

Additionally, there have been documented instances of discrepancies in *SMN2* copy number between initial and re-determined testing; factors affecting accuracy of *SMN2* copy number quantification included sample contamination, obtaining sufficient quality and quantity of DNA, availability and use of appropriate controls, and definition of cut-off values.[24] Should a copy number threshold be used to

determine treatment course there may be patients with severe forms of SMA who do not receive treatment in the pre-symptomatic period and hence do not benefit from screening. Conversely, there may be patients with less severe forms of SMA who receive a treatment or, in a small number of cases, a diagnosis, that would not be provided in the absence of screening. The potential resource and ethical implications of such decision-making are explored in chapters 7 and 8 of this HTA.

4 Clinical effectiveness of screening

Key points

- The purpose of this chapter is to describe the clinical effectiveness of population-based newborn bloodspot screening programmes for spinal muscular atrophy (SMA). To facilitate this, a systematic review of the approaches used internationally, and the outcomes of these programmes, was undertaken.
- Thirty-two publications, describing 20 unique studies, were included and categorised as:
    - Non-comparative studies (n = 17): these were descriptive studies, providing details of the approach used in programmes and of outcomes such as test performance, SMA case characteristics, incidence, and potential harms; studies did not compare to unscreened cohorts.
    - Comparative studies (n = 3): these studies presented clinical outcomes (for example, morbidity) of screened and unscreened cohorts.
- Of the 17 studies providing detail on approaches used, the primary target of screening in all studies was homozygous deletions in survival motor neuron 1 (*SMN1)* using polymerase chain reaction (PCR)-based methods as the initial test. However, there was variation in the use of second tier tests, test targets, confirmatory testing methods, and laboratory techniques.
    - Eight studies included a second tier test to confirm *SMN1* deletions and or quantify survival motor neuron 2 *(SMN2)* gene copy number. The latter was highlighted as enabling early treatment planning in a number of studies, but in two studies represented a cut-off for screen positives. In both such studies, the use of *SMN2* cut-offs for test positivity (< 4 or < 5 copies) was related to the uncertainty associated with the prognostic value of higher copy numbers.
- Considering test performance, the following measures were calculated across 16 included studies:
    - Referrals for confirmatory testing as a percentage of the total population screened: ranged from < 0.01% to 0.14% with the midpoint being 0.01% (that is, 1 in 10,000).
    - Positive predictive value: ranged from 16.67% to 100% with the midpoint being 100% and with 13 studies having a value at or above

90%. As a percentage of the total population screened, this reflected a false positivity rate of less than 0.01% (< 1 in 10,000) in all but one study (0.12%). Based on pooled data across the 16 studies which reported false positivity rates, the ratio of SMA cases to false positive cases was 6:1.

- In the case of two studies with relatively higher instances of false positives, a conservative laboratory cut-off and the collection of samples from acutely unwell infants were cited as possible causes.

- A limited number of undetected SMA cases (false negatives) were reported across the included studies with none considered to be directly reflective of the test used, but instead being related to variants which are not the target of screening (that is, they are not homozygous deletions) and human or system errors in reporting.

- Collectively, of approximately 3.2 million infants screened, 240 cases of SMA were identified through screening.
  - The majority of these cases had two (n = 118, 49%) or three (n = 71, 30%) copies of *SMN2*.
  - Symptom status was reported for 212 cases with 68 (32%) noted to be symptomatic at some point within the screening pathway up to and including treatment initiation. The majority of these cases had two copies of *SMN2* (n = 51, 75%).
- The reported incidence rate of SMA associated with homozygous deletions ranged from 1 in 6,059 to 1 in 19,000 (midpoint 1 in 13,500) across the studies. Considering the total number of SMA cases detected and the total number of infants screened in these studies, a collective incidence of 1 in 14,574 is estimated. The impact of screening on incidence cannot be accurately assessed given the short time periods for which screening has been implemented.
- Limited data were identified from three studies on the impact of newborn bloodspot screening on morbidity, with all three presenting a potential positive impact. One study explicitly compared outcomes in a screened cohort with an unscreened cohort, with evidence to suggest significantly improved functional outcomes with screening. However, this study included very few cases with four or more *SMN2* copies.

- While providing promising results of the effect of newborn bloodspot screening on clinical outcomes, these studies included small sample sizes, were restricted to a maximum of two years of follow-up data, and will be inherently linked to the long term effectiveness data of disease-modifying treatments, which is also limited at present. However, these studies represent the best available evidence for the effectiveness of screening on clinical outcomes currently in the context of a rare disease.
- With respect to consideration of the potential harms of screening:
    - Factors noted in studies included not detecting SMA cases caused by compound heterozygous variants in *SMN1* (while not the target of this form of screening it has implications for the informed consent process and vigilance of symptoms), the clinical uncertainty surrounding outcomes in those with higher *SMN2* copy numbers, and the potential for psychological impact on the screened individual and their family.
    - While not noted within the studies identified, any requirement for a separate blood draw to perform confirmatory testing may represent a potential harm as families may be contacted for what is subsequently confirmed as a false positive result. Decisions on sample requirements (blood spot or a separate venous blood draw) would be taken at the laboratory verification stage prior to implementation.

4.1 Introduction

Screening is used to identify individuals from an apparently healthy, asymptomatic, population who are at higher risk of a particular condition.[124] The overall aim of screening is the provision of an early treatment or intervention to enable better outcomes than if the individual presented symptomatically or later in the disease course.[124] Rather than comprising an isolated test, screening typically involves a detailed pathway, which includes:[124]

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

The aim of this chapter is to describe the clinical effectiveness of newborn bloodspot screening for spinal muscular atrophy (SMA). This aim is facilitated through a systematic review of the international literature of approaches to, and outcomes of, newborn bloodspot screening for SMA. The term 'clinical effectiveness' encompasses National Screening Advisory Committee (NSAC) criteria (see Appendix Chapter 1, Table A1.1) relating to:

- The screening method: the method should be simple, safe, precise, reliable, and validated. The distribution of screening values should be assessed and suitable cut-off levels or measurements defined and agreed. The process should be acceptable to the target population.

- The screening programme: there should be evidence that the screening programme is effective in reducing mortality or morbidity. Where screening is aimed solely at providing information to enable informed choice, there must be evidence from high quality trials that the test accurately measures risk.

NSAC criteria relating to treatment are discussed in detail in chapter 5 (overview of treatments); however, policies on decision-making for the treatment of patients identified through screening are summarised where described by the included studies.

4.2 Methodology for review of clinical effectiveness

A protocol detailing the methods undertaken in this review has been published previously (available here) and also registered on PROSPERO (CRD42023418944).

The reporting of this systematic review adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria.[125]

4.2.1 Review question

As outlined in Table 4.1, the review question was formulated according to the Population, Intervention, Comparator, Outcome (PICO) framework. The review seeks to answer the following question:

- What are the approaches used internationally for population-based newborn bloodspot screening programmes for SMA and what are the outcomes of these programmes?

The approaches to newborn bloodspot screening of interest include descriptions of screening algorithms, test methodologies, and treatment pathways. The outcomes of interest include measures of test performance, pathway timings, incidence, clinical outcomes (mortality and morbidity), potential harms, and acceptability.

Table 4.1 Review question for assessing clinical effectiveness of newborn bloodspot screening for SMA

Population	Newborns
Intervention	Population-based newborn bloodspot screening for SMA.
Comparator	▪ No population-based newborn bloodspot screening for SMA (SMA cases identified clinically). ▪ No comparator (outcomes of screening cohort only described).
Outcomes	Non-comparative studies: ▪ test performance ▪ case characteristics (for example, *SMN2* copy number, symptom status) ▪ pathway timings (for example, time to diagnosis) ▪ harms. Comparative studies: ▪ clinical outcomes (for example, mortality and morbidity) ▪ pathway timings (for example, time to diagnosis) ▪ harms.
Study design	Include: ▪ Case-control, cohort studies, and cross-sectional studies. Exclude: ▪ Non-human studies; studies of analytical performance; studies without SMA cases detected; papers not available in English; letters, editorials, commentaries, preprints, and conference abstracts.

Key: SMA – spinal muscular atrophy; *SMN2* - survival motor neuron 2 gene.

4.2.2 Types of studies

Cohort, case-control, and cross-sectional studies of population-based newborn bloodspot screening for SMA were considered eligible for inclusion. Both comparative studies (which compare clinical outcomes based on the intervention of screening) and non-comparative studies (which report outcomes for population-based newborn bloodspot screening and contribute descriptive information on outcomes such as test performance) of population-based newborn bloodspot screening for SMA were considered eligible.

4.2.3 Population of interest

The population of interest were newborns partaking in newborn bloodspot screening for SMA (with or without other newborn bloodspot tests).

4.2.4 Intervention of interest

The intervention of interest was newborn bloodspot screening for SMA. The approaches to newborn bloodspot screening that were of interest included descriptions of screening algorithms, test methodologies, and treatment pathways.

4.2.5 Comparator of interest

For comparative studies, the comparator of interest was no population-based newborn bloodspot screening for SMA.

4.2.6 Outcomes of interest

The outcomes of interest to this systematic review were documented measures of clinical effectiveness. The outcomes of interest varied according to the study design:

Non-comparative studies:

- test performance (for example, positive predictive value)
- case characteristics (for example, survival motor neuron 2 *(SMN2)* gene copy number, symptom status)
- pathway timings (for example, time to diagnosis)
- incidence
- harms
- acceptability.

Comparative studies:

- clinical outcomes (for example, mortality and morbidity)
- pathway timings (for example, time to diagnosis)
- harms

- acceptability.

Clinical outcomes were not included for non-comparative studies as, in the absence of a relevant comparator, it would not be possible to distinguish the effect of the screening programme from the effect of treatment and care of the patient with SMA.

4.2.7 Exclusion criteria

The following exclusion criteria were applied:

- studies of analytical performance in which both clinical samples and controls (that is, known SMA cases) were assessed in combination, or where the study's aim was to validate the testing method only
- studies without SMA cases detected
- non-human studies
- studies that were not available in the English language
- editorials, commentary, review articles, pre-prints, letters, and conference abstracts.

4.2.8 Search strategy

A collective search strategy was developed for the present systematic review and the systematic review of cost effectiveness outlined in chapter 6. Electronic searches were conducted between 24 January 2023 and 1 February 2023 in Medline (EBSCO), Embase (Elsevier), the Cochrane Library (Wiley), ClinicalTrials.gov, and the World Health Organization International Clinical Trials Registry Platform, supplemented by a grey literature search. Search alerts were set up and periodically checked over the course of the review period for newly published literature. 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).

4.2.9 Study selection and data extraction

Study selection

Following the removal of initial duplicates in EndNote, returned citations from the collective search were added to Covidence for reference management. 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 piloted prior to the undertaking of the review. Data extraction was performed by one reviewer, and cross-checked by a second reviewer with discrepancies resolved by consensus and the involvement of a third reviewer where required. In the case of missing data relating to study populations and outcomes, the study authors were contacted

4.2.10 Data synthesis

A narrative synthesis was undertaken structured by the outcomes of interest to this review and sectioned by study type (that is, non-comparative and comparative studies), where applicable.

4.2.11 Quality appraisal

No validated quality appraisal tool was identified that was considered appropriate to the types of studies included in this systematic review. As such, *de novo* checklists were developed for the two study types, comparative and non-comparative. The checklists were piloted and subsequently completed independently by two reviewers, with discrepancies resolved by consensus and the involvement of a third reviewer where required.

4.3 Results

4.3.1 Search results

As highlighted previously, a collective search strategy was developed for the present systematic review and the systematic review of cost effectiveness outlined in chapter 6. The number of research articles screened, assessed for eligibility, and included in each review are presented in the PRISMA flow diagram of search results in Appendix Chapter 4, Figure A4.1. The collective search returned 893 citations. Following duplicate removal, the titles and abstracts of 637 citations were screened with 88 full texts assessed for eligibility. Based on the defined exclusion criteria, 51 citations were excluded. Thirty-seven articles were deemed eligible with 32 being of relevance to the present review and five included in the systematic review of cost effectiveness described in chapter 6.

Following an overview of the included study characteristics, the results of this systematic review are structured as follows:

Approaches to newborn bloodspot screening programmes for SMA

- screening algorithms

- treatment pathways.

Outcomes of newborn bloodspot screening programmes for SMA

- test performance
- characteristics of SMA cases detected through newborn bloodspot screening
- pathway timings
- incidence
- clinical outcomes
- potential harms of screening
- acceptability.

4.3.2 Study characteristics

Of the 32 articles included in the present review,[7, 47, 52, 69, 81, 126-152] 29 publications were considered to present non-comparative cohort studies of newborn bloodspot screening for SMA (that is, no comparator was presented). These publications were typically descriptive in nature, providing details of the approach used in programmes and of outcomes such as test performance.[7, 47, 52, 69, 81, 126-129, 131, 132, 134-136, 138-152] The remaining three were comparative studies, that is, they presented clinical outcomes (for example, morbidity) of screened and unscreened cohorts.[130, 133, 137]

4.3.2.1 Non comparative studies

Of the 29 included non-comparative publications,[7, 47, 52, 69, 81, 126-129, 131, 132, 134-136, 138-152] 17 were considered to present unique cohort data.[52, 69, 81, 126, 127, 134, 135, 139, 141-145, 147, 148, 151, 152] The remaining 12 publications were found to represent duplications of populations included by primary studies within the review and hence were not included as individual studies, but assessed for any additional information of relevance only.[7, 47, 128, 129, 131, 132, 136, 138, 140, 146, 149, 150]

The characteristics of the included studies are presented in Table 4.2. Of the 17 unique cohorts presented, nine were outlined as being from pilot programmes,[52, 69, 81, 126, 141, 142, 144, 147, 151] four were implemented population-level screening programmes,[127, 135, 143, 145] three included data from pilot programmes that transitioned into population-level programmes,[134, 139, 152] and one was unclear as to the nature of the programme.[148]

Collectively, across all included studies, data were presented for 3,178,517 infants screened for SMA. The median duration of the screening programmes was 24 months ranging from three months[144] to 60 months,[152] with the earliest reported year being 2014 and the majority of studies beginning after 2017. Seven cohorts

were from the US (California, Georgia, Massachusetts, New York, North Carolina, and Wisconsin),[127, 134, 135, 141-143, 145] two were from Japan (Hyogo and Kumamoto prefectures),[147, 148] with one each from Australia (New South Wales and Australian Capital Territory),[81] Belgium (southern region),[52] Canada (Ontario),[139] China (six maternity hospitals),[144] Germany (Bavaria and North Rhine-Westphalia),[151] Italy (Lazio and Tuscany),[126] Latvia, and Taiwan (one screening centre).[152]

Three studies reported the timing of sample collection to be 48 to 72 hours after birth,[69, 81, 126] two at 96 to 144 hours,[147, 148] and one each at 12 to 48 hours,[145] 24 to 48 hours,[139] and 48 to 120 hours.[52] Nine studies did not report the timing of dried bloodspot (DBS) collection.[127, 134, 135, 141-144, 151] For context, DBS as part of the Irish programme are collected 72 to 120 hours after birth.

4.3.2.2 Comparative studies

The characteristics of the three comparative studies are presented in Table 4.3.

The study from Australia was a prospective non-randomised cohort study with historical comparison.[153] This study aimed to investigate the effectiveness of newborn bloodspot screening coupled with disease-modifying treatments as an intervention for SMA. The screened cohort included 15 cases of SMA aged up to 16 years with a homozygous survival motor neuron 1 *(SMN1)* deletion born in the first two years (1 August 2018 to 1 August 2020) of a pilot screening programme (this screened cohort represented a subset of the population described in a previously published non-comparative study).[81] The comparator cohort was a historical group of 18 patients with SMA diagnosed following clinical referral with signs and symptoms of SMA that presented consecutively in the two years prior to the pilot screening programme (1 August 2016 to 31 July 2018). Outcomes were assessed at two years post diagnosis for those who survived (n = 14/15 (93%) in the screening group and n = 16/18 (89%) in the comparator group).

The study undertaken across Belgium, France, and Germany was a cross-sectional study of combined data from two prospective cohort studies.[154] The study aimed to assess and compare quality of life and costs of untreated patients with SMA and treated patients with SMA identified by symptoms or other means (family history and newborn bloodspot screening), to evaluate potentials benefits. There were 14 in the group not identified by symptoms (10 from newborn bloodspot screening and four from family history), 42 in the treated symptomatic group, and 93 in the untreated symptomatic group, with up to two years of follow-up data available. Results were not presented separately by identification method within this group. However, for the purposes of this review, identification by family history was considered a proxy for identification by newborn bloodspot screening.

The study from Hong Kong, South Korea and Taiwan, was a retrospective cohort study.[130] The study aimed to provide real-world data on patients with type I SMA treated with nusinersen for at least one year. While not explicitly comparing outcomes of screened versus unscreened cohorts, the study included regression analyses of outcomes with newborn bloodspot screening included as a variable of interest. There were nine patients with SMA identified by newborn bloodspot screening, and 31 not identified by screening.

Table 4.2 Characteristics of non-comparative studies

Study	Country (Region)	Programme type	Population	Study duration	Total screened
Abiusi 2022[126]	Italy (Lazio and Tuscany)	Pilot	Newborns born in 54 of the 55 regional birth centres DBS collected 48 to 72 hours after birth	5 September 2019 to 4 September 2021 24 months	90,885
Baker 2022[127]	United States (Wisconsin)	Population-level	Newborns born in Wisconsin state	15 October 2019 to 14 October 2020 12 months	60,984
Boemer 2021[52] Additional reporting: Boemer 2019[128] and Boemer 2019b[129]	Belgium (Southern region)	Pilot	2018: All maternity hospitals located in Liège, and the majority in Luxembourg and Namur included. Early 2019: Extended to include all newborns in Southern Belgium. DBS collected 48 to 120 hours after birth.	March 2018 to February 2021 36 months	136,339
D'Silva 2022[81] Additional reporting: Kariyawasam 2020[136]	Australia (New South Wales and the Australian Capital Territory)	Pilot	Newborns born in New South Wales and the Australian Capital Territory DBS collected 48 to 72 hours after birth	August 2018 to January 2021 29 months	252,081

Study	Country (Region)	Programme type	Population	Study duration	Total screened
Elkins 2022[134]	United States (Georgia)	Initially pilot based and transitioned into standard screening at the population level	Newborns born in Georgia state	February 2019 to February 2020: Pilot February 2020 to February 2021: Population-level 24 months	301,418
Gailite 2022[69]	Latvia	Pilot	All maternity wards and hospitals in Latvia DBS collected 48 to 72 hours after birth	February 2021 to November 2021 9 months	10,411
Hale 2021[135]	United States (Massachusetts)	Population-level	Newborns born in Massachusetts state	27 January 2018 to 31 January 2021 36 months	179,467
Kernohan 2022[139] Additional reporting: McMillan 2021[47]	Canada (Ontario)	Pilot basis in January 2020, implemented on a permanent basis in July 2020	Newborns in Ontario. DBS 24 to 48 hours after birth	Precise dates not provided. 12 months	139,800
Kraszewski et al 2018[141]	United States (New York)	Pilot*	Weekday recruitment with defined inclusion criteria at three hospitals in New York State	January 2016 to January 2017 12 months	3,826

Study	Country (Region)	Programme type	Population	Study duration	Total screened
Kucera 2021[142]	United States (North Carolina)	Pilot	Newborns enrolled in study prenatally or postnatally: representing approximately 5% of all newborns in the state and some surrounding states.	October 2018 to December 2020 26 months	12,065
Lee 2022[143] Additional reporting: Kay 2020[138]	United States (New York)	Population-level	Newborns born in New York State	October 2018, to September 2021 36 months	650,000
Lin 2019[144]	China	Pilot	Newborns born in six specific hospitals	March 2018 to June 2018 Three months	29,364
Matteson 2022[145]	United States (California)	Population-level	Newborns born in California state DBS 12 to 48 hours after birth	24 June 2020 to 23 December 2021 18 months	628,791
Noguchi 2022[147]	Japan (Hyogo Prefecture)	Pilot	22% of all prefecture births DBS collected 96 to 144 hours after birth	February 2021 to August 2022 18 months	8,336

Study	Country (Region)	Programme type	Population	Study duration	Total screened
Sawada 2022[148]	Japan (Kumamoto Prefecture)	Unclear	96% of all births in prefecture DBS collected 96 to 144 hours after birth	February 2021 to January 2022 12 months	13,587
Vill 2021[151] Additional reporting: Vill 2019,[150] Czibere 2020,[132] Muller-Felber 2020,[146] Schwartz 2022,[149] Kolbel 2022[140]	Germany (Bavaria and North Rhine-Westphalia)	Pilot from January 2018 to May 2019 which continued thereafter on the authors' own initiative	Screening laboratory covers approximately 78% of newborns in Bavaria and 37% in North Rhine-Westphalia. Six initial non-participating hospitals that reduced to one over the course of study period.	January 2018 to January 2020 24 months	297,163
Weng 2021[152] Additional reporting: Chien 2017[131]	Taiwan (one screening centre)	Pilot followed by population-level implementation	National Taiwan University Hospital Newborn Screening Centre which routinely screens 35%-37% of the newborns born in Taiwan	November 2014 to September 2016: Pilot September 2016 to December 2019: Population-level 60 months	Pilot: 120,267 Total: 364,000

Key: DBS – dried bloodspot.
* Pilot programme prior to implementation at population-level described by Lee et al.[143]

Table 4.3 Characteristics of comparative studies

Study	Country	Study design	Outcomes	Follow-up	Population
Kariyawasam 2023[153]	Australia (New South Wales and Capital Territory)	Prospective non-randomised cohort study with historical comparison	Functional ability: ▪ Walking ability ▪ HINE-II ▪ WeeFIM ▪ WHO motor milestones Nutrition and non-invasive ventilation support	Two-years post diagnosis for survivors	Screened group (n = 15): ▪ Homozygous *SMN1* deletion ▪ Born in first two years of the pilot screening programme (August 1, 2018 to August 1, 2020)[81] ▪ Excluded patients with SMA participating in ongoing, unpublished clinical trials Comparator group (n =18): ▪ Patients with SMA diagnosed following clinical referral with signs and symptoms of SMA ▪ Consecutively presenting in the two years prior to screening (August 1, 2016 to July 31, 2018)
Dangoulouff 2022[154]	Belgium, Germany, and France	Cross-sectional study of combined data from two prospective cohort studies	Quality of life	Up to 2 years	▪ Not identified by symptoms: n = 14 (10 from newborn bloodspot screening and 4 from family history) ▪ Treated symptomatic patients: n = 42 ▪ Untreated symptomatic patients: n = 93
Chan 2021[130]	Hong Kong, Taiwan, and South Korea	Retrospective cohort study	Associations (including screening) with HINE-II and CHOP-INTEND scores	One-year post start of nusinersen treatment	Patients with SMA from 8 institutes with SMA type 1 and who had been receiving nusinersen for at least one year ▪ Identified by newborn bloodspot screening: n = 9 ▪ Not identified by newborn bloodspot screening: n = 31

Key: CHOP-INTEND - Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; HINE - Hammersmith Infant Neurological Examination; SMA – spinal muscular atrophy; *SMN1* – survival motor neuron 1 gene; WeeFIM – Functional Independence Measure for Children; WHO – World Health Organisation.

4.3.3 Approach: Screening algorithms

Details of screening algorithms were provided by non-comparative studies only; the methodologies and algorithms used by these are outlined in Appendix Chapter 4, Table A4.1. The target of screening in all included studies was homozygous deletions in *SMN1*, with the majority citing deletions in exon 7 specifically. One pilot study from New York further sought to identify carriers of the *SMN1* exon 7 deletion; this approach was discontinued when screening was implemented at the population level as reported in a subsequent study.[141, 143]

Nine studies used single tier testing,[69, 126, 134, 141, 142, 144, 147, 148, 151] seven used two tier testing,[52, 81, 127, 139, 143, 145, 152] and one study included three tiers.[135] Fifteen studies used quantitative PCR (qPCR) as the first tier with three citing the use of commercial kits,[81, 147, 148] five studies citing the use of a US CDC-developed assay,[69, 134, 135, 142, 145] and the remaining studies reporting the use of locally developed assays or being unclear as to the assay nature.[52, 126, 127, 141, 143, 151, 152] The cycle threshold cut-off (that is, a threshold defined by the laboratory during verification to indicate screen positives) was reported in seven studies and ranged from 26 to 36 cycles.[126, 134, 141-143, 145, 151] The two remaining studies used MassARRAY as the first tier (that is, a specific technology coupling end-point PCR with mass spectrometry to enable multiplexing of many newborn bloodspot screening conditions).[139, 144] Four studies further highlighted that the assay in use was multiplexed for other newborn bloodspot screening conditions, most commonly SCID.[81, 127, 134, 139]

Of eight studies including a second tier, five used digital droplet PCR (ddPCR),[81, 127, 143, 145, 152] one used qPCR,[135] and two used multiplex ligation-dependent probe amplification (MLPA).[52, 139] Five of these studies used the second tier to confirm *SMN1* deletions and quantify *SMN2* copy number,[52, 135, 139, 145, 152] and three cited quantification of *SMN2* copy number only.[81, 127, 143] Of these studies, two further included cut-offs for screen positives based on *SMN2* copy numbers alongside homozygous *SMN1* deletion. A Canadian study used a threshold of less than five *SMN2* copies.[139] An Australian study of a pilot programme initially a used a cut-off of less than four copies,[81] but subsequently amended the program by removing the cut-off and subsequently captured all cases with homozygous *SMN1* deletions regardless of copy number. It is unclear at what time point the change occurred.[155]

Referral and confirmatory testing for screen positives was reported in all studies; MLPA was specified as the technique used in eight studies,[52, 69, 81, 142, 144, 148, 151, 152] PCR in two studies,[126, 145] ddPCR in two studies,[127, 147] and the technique being unclear in the remaining five studies.[134, 135, 139, 141, 143]

4.3.4 Approach: Treatment pathways

The treatment pathways used for SMA cases detected through newborn bloodspot screening in the included studies are outlined in Appendix Chapter 4, Table A4.2. As shown, the pathways presented varied across studies and were largely contingent on the drugs available through clinical trials or licensed for use (subject to reimbursement criteria) in the local context. Of five studies reporting a basis for decision-making on treatments, three cited the use of recommendations from the American SMA Newborn Bloodspot Screening Multidisciplinary Working Group outlined in section 2.3.3,[52, 135, 151] and two cited the use of local multidisciplinary consensus groups.[81, 139] The inclusion of genetic counselling and family decision-making was cited in the eight of the included studies.[81, 126, 127, 134, 139, 141, 142, 145]

The treatment status of SMA cases across the included studies is reported in Appendix Chapter 4, Table A4.3.

4.3.5 Outcome: Test performance

Background to measures of test performance

As outlined previously, screening is distinct from diagnosis, and positive screening tests typically require onward referral for confirmatory testing and subsequent diagnosis. Within the context of a screening programme, the concept of further testing following a positive screening test, in order to establish a diagnosis, is referred to as 'confirmatory testing'. Confirmatory testing may also rule out the presence of a condition, resulting in a 'false positive' result being returned for the screening test. Measures of newborn bloodspot screening test performance at the population level are somewhat restricted given that only those with a positive screening test result proceed to confirmatory testing. In this way, cases with a negative screening test result may still present later symptomatically and not be captured within the study period (false negative tests). This is particularly relevant in SMA, whereby children with type III and type IV may present clinically anytime from 18 months of age into adulthood. In this context, the following measures of test performance calculated from the included studies are presented:

- Referral rate: the percentage of all newborns screened that are referred and complete confirmatory testing:
    - Referral rate = [number of newborns referred and completing confirmatory testing/total population screened]*100
- Positive predictive value (PPV): the likelihood that when a test result is positive the person truly has the condition. Presented as a percentage:

  - PPV = [(newborns correctly identified as SMA) / (number with completed confirmatory testing)]*100

- False positivity: the number of newborns referred for confirmatory testing who were not found to have SMA. Presented as two percentages:
  - False positivity (of referred population) = [(number of newborns with abnormal screens who subsequently have normal confirmatory testing)/(number with completed confirmatory testing)]*100
  - False positivity (of total population screened) = [(number of newborns with abnormal screens who subsequently have normal confirmatory testing)/(total population screened)]*100
- Documented undetected cases: Any cases of SMA that were documented by study authors as undetected during newborn bloodspot screening who were subsequently identified by symptomatic presentation.

These measures of test performance, alongside the high-level elements of the screening algorithm, for each study are presented in Table 4.4 and elaborated below.

Referrals

As a percentage of the total population screened, the rate of referral for completed confirmatory testing ranged from 0.004% in the Ontario region of Canada[139] to 0.14% in a pilot study from the Hyogo Prefecture in Japan,[147] with the midpoint across all studies being 0.01% (1 in 10,000 screened). To note, studies typically did not report the number initially referred for confirmatory testing and whether this differed from the number completing confirmatory testing.

Positive predictive value

The PPV across the 16 included studies in which it could be calculated ranged from 16.67% from the pilot study in the Hyogo Prefecture in Japan[147] to 100% in 10 studies.[52, 69, 127, 139, 141, 143, 145, 148, 151, 152] The midpoint calculated PPV across all included studies was 100% with the PPV in 13 studies being at, or above, 90%.

False positives

As a percentage of the total population screened, the false positivity rate (for 16 included studies in which it could be calculated) was less than 0.01% (< 1 in 10,000 screened) in all but one study from the Japanese Hyogo Prefecture (0.12%).[147] The ratio of SMA cases to false positive cases was 6:1. As a percentage of those referred for confirmatory testing, the false positivity rate ranged from 0% in 10 studies,[52, 69,

[127, 139, 141, 143, 145, 148, 151, 152] to 83.33% in the pilot study from the Hyogo Prefecture in Japan.[147] Contextual details underlying these results are discussed below.

Of studies reporting false positive results, the Japanese pilot from the Hyogo Prefecture reported the highest proportion of those referred for confirmatory testing (83.33%).[147] The authors noted that all false positive cases were from hospitals that provided medical care for acutely unwell newborns where intravenous infusion and the heparinisation of blood products would be commonplace. Blood in these cases was typically drawn from catheters which are intermittently flushed with heparinised saline. The rate of false positives was noted to decrease after obstetricians and neonatologists were requested not to use heparinised blood for newborn bloodspot screening samples. A second outlier in results was from a screening programme in Georgia State in the US with 24 out of 39 referrals noted to be false positives.[134] The authors highlighted that a proportion were in the initial pilot phase after which the cycle threshold (Ct) cut-off was modified to reduce false positives. The authors also noted that a proportion of false positive results were samples from acutely unwell children in neonatal intensive care unit settings, with the suggestion that the false positive results for these cases may have correlated with a low white blood cell count.

Single instances of false positives were reported in four other studies.[81, 126, 135, 142] Following genetic analysis, one instance was found to be related to a variant of unknown significance in *SMN1*,[81] one was a mosaic *SMN1* homozygous loss (that is, when an individual's cells have multiple genetic makeups),[126] one original sample was suggested to contain a PCR inhibitor,[135] and one was noted to be an infant who was subsequently diagnosed with Shwachman-Diamond Syndrome, a rare genetic disorder that affects bone marrow and the generation of white blood cells, for whom Ct values of the initial screen were considered to be borderline.[142]

Documented undetected cases

Eight studies explicitly reported that no undetected cases of SMA resulting from homozygous deletions in *SMN1* had been noted during the study period.[52, 69, 126, 135, 139, 145, 148, 151] Four cases of SMA were documented as being undetected during study periods due to factors unrelated to screening test performance; these included one parental refusal of screening,[126] one screen positive that was not reported due to human error,[134] one case that did not have SMA testing completed as part of newborn bloodspot screening due to a systems error,[81] and one for whom a DBS sample was not received by the screening laboratory.[81] While not the target of screening, two studies reported cases of SMA resulting from compound heterozygous variants (that is, deletion on one allele and point mutations on the other) that were clinically identified over the study period.[52, 152]

Again, it should be noted that the documented undetected cases may underestimate the true number given that newborns screened are not systematically followed up, the limited study durations, and the fact that cases of SMA may present clinically into adulthood.

Table 4.4 Measures of test performance calculated from included studies

Study	First tier	Second tier	Total screened	Total completed referrals (% of screened)	SMA cases	False positives	False positives (% of referred)	False positives (% of screened)	PPV
Abiusi 2022[126]	qPCR	NA	90,885	16 (0.02%)	15	1	6.25%	< 0.01%	94%
Baker 2022[127]	qPCR	ddPCR	60,984	6 (0.01%)	6	0	0%	0%	100%
Boemer 2021[52, 128, 129]	qPCR	MLPA	136,339	9 (0.01%)	9	0	0%	0%	100%
D'Silva 2022[81, 136]	qPCR	ddPCR (≤ 3 *SMN2* copies)	252,081	22 (0.01%)	21	1	4.55%	< 0.01%	95.45%
Elkins 2022[134]	qPCR	NA	301,418	39 (0.01%)	15	24	61.54%	< 0.01%	38.46%
Gailite 2022[69]	qPCR	NA	10,411	2 (0.02%)	2	0	0%	0%	100%
Hale 2021[135]	qPCR	qPCR	179,467	10 (0.01%)	9	1	10%	< 0.01%	90%
Kernohan 2021[47, 139]	MassARRAY	MLPA (≤ 4 *SMN2* copies)	139,800	5 (< 0.01%)	5	0	0%	0%	100%

Study	First tier	Second tier	Total screened	Total completed referrals (% of screened)	SMA cases	False positives	False positives (% of referred)	False positives (% of screened)	PPV
Kraszewski et al 2018[141]	qPCR	NA	3,826	1* (0.03%)	1	0*	0%*	0%*	100%
Kucera 2021[142]	qPCR	NA	12,065	2 (0.02%)	1	1	50%	< 0.01%	50%
Lee 2022[138, 143]	qPCR	ddPCR	650,000	34 (0.01%)	34	0	0%	0%	100%
Lin 2019[144]	MassARRAY	NA	29,364	NR	3	NR	NR	NR	NR
Matteson 2022[145]	qPCR	ddPCR	628,791	34 (0.01%)	34	0	0%	0%	100%
Noguchi 2022[147]	qPCR	NA	8,336	12 (0.14%)	2	10	83.33%	0.12%	16.67%
Sawada 2022[148]	qPCR	NA	13,587	1 (0.01%)	1	0	0%	0%	100%
Vill 2021[132, 140, 146, 149-151]	qPCR	NA	297,163	43 (0.01%)	43	0	0%	0%	100%
Weng 2021[131, 152]	qPCR	ddPCR	364, 000	NR	20	0**	0%	0%	100%

Key: ddPCR – digital droplet polymerase chain reaction; MLPA – multiplex ligation-dependent probe amplification; NA – non-applicable; NR – not reported; PPV – positive predictive value; qPCR – quantitative polymerase chain reaction; SMA – spinal muscular atrophy; *SMN2* – survival motor neuron 2 gene.
* Excludes carriers detected as a separate target of screening pilot (n = 59).
** First tier qPCR detected 8 false positives in pilot study.

4.3.6 Outcome: Characteristics of SMA cases detected through newborn bloodspot screening

Collectively, across the 17 included non-comparative studies, 240 cases of SMA were reported (including 19 additional cases reported from unpublished data provided by the Ontario study authors from an additional 254,499 newborns screened since the publication of the original study[139, 156]). The characteristics of identified cases are presented below; these include *SMN2* copy number, symptom status, family history, and results of cascade testing (that is, the testing of family members for a genetic condition following identification of an index case).

SMN2 copy number

The *SMN2* copy number for cases identified through newborn bloodspot screening across the included studies is presented in Table 4.5.

Of the 240 collective cases of SMA identified by the included screening programmes, the proportions of *SMN2* copy number were calculated as (to note, a number of studies grouped copy numbers above four so these are reported as per groupings used):

- One copy of *SMN2*: 2.1% cases (n = 5)
- Two copies of *SMN2*: 49.2% cases (n = 118)
- Three copies of *SMN2*: 29.6% cases (n = 71)
- Four or more copies of *SMN2*: 19.2% cases (n = 46)
    - Four copies: 12.9% cases (n = 31)
    - Four or more copies: 5.0% cases (n = 12)
    - Five or more copies: 1.3% cases (n = 3).

Two screening programmes included a cut-off of *SMN2* copy number (less than four and five copies respectively) in their definition for screen positives; this may affect the representativeness of the sample (that is, not all screening tests with *SMN1* deletions are included).[81, 139] Excluding these studies, 195 cases of SMA were reported with the following proportions of *SMN2* copy number:

- One copy of *SMN2*: 2.6% cases (n = 5)
- Two copies of *SMN2*: 47.2% cases (n = 92)
- Three copies of *SMN2*: 28.2% cases (n = 55)
- Four or more copies of *SMN2*: 22.1% cases (n = 43)
    - Four copies: 14.4% cases (n = 28)
    - Four or more copies: 6.2% cases (n = 12)
    - Five or more copies: 1.5% (n = 3).

Table 4.5 *SMN2* copy numbers of SMA cases

Study	Number of SMA cases	Cases by *SMN2* copy number				
		1 copy	2 copies	3 copies	4 copies	5+ copies
Abiusi 2022[126]	15	1	9	3	1	1
Baker 2022[127]	6	-	2	2	2	-
Boemer 2021[52, 128, 129]	9	-	4	3	2	-
D'Silva 2022[81, 136]	21	-	12	8	1**	NA
Elkins 2022[134]	16^	2	5	7	2*	NR
Gailite 2022[69]	2	1	-	1	-	-
Hale 2021[135]	9	-	7	-	2	-
Kernohan 2021[139, 156]	24	-	14	8	2	NA
Kucera 2021[142]	1	-	1	-	-	-
Lee 2022[138, 143]	34	1	18	11	4*	NR
Lin 2019[144]	3	-	2	-	1	-
Matteson 2022[145]	34	-	16	12	6*	NR
Noguchi 2022[147]	2	-	2	-	-	-
Sawada 2022[148]	1	-	-	1	-	-
Vill 2021[132, 140, 146, 148, 150, 151]	43	-	17	10	14	2
Weng 2021[131, 152]	20¥	-	9	5	6	-

Key: NA – non-applicable (studies include *SMN2* cut off for screen positives); NR – not reported; SMA – spinal muscular atrophy.
* Study reported "four or more copies".
** 4 copies *SMN2* originally quantified as 3 copies in screening test but identified as 4 copies in confirmation testing.
^ Includes additional case not reported in screening due to human error.
¥ Excludes results of one compound heterozygous variant not detected through screening.

Symptom status

As outlined in Table 4.6, fifteen studies reported the symptom status of SMA cases detected through newborn bloodspot screening.[52, 69, 81, 126, 134, 135, 139, 141-143, 145, 147, 148, 151, 152] The included studies varied in terms of the time point at which symptom status was reported, with four reported at the first clinical visit,[126, 134, 135, 142] three at diagnosis,[69, 147, 148] three at the first four weeks of life,[81, 151, 152] three at treatment initiation,[52, 143, 145] and two reporting status at both diagnosis and treatment initiation.[139, 141] Across all time points reported, of 212 SMA cases, 68 (32%) were reported to be symptomatic (19 at first clinical visit, two at diagnosis, 22 in the first four weeks of life, and 25 at treatment initiation) with the majority of

these cases having two *SMN2* copies (n = 51, 75.0%). The remaining reported symptomatic cases had one *SMN2* copy (n = 4, 5.9%), three *SMN2* copies (n = 4, 5.9%), four *SMN2* copies (n = 2, 2.9%), and one case was cited as being type 0 without a copy number provided. Six symptomatic cases (8.8%) did not have a copy number reported.

Table 4.6 Symptom status of identified SMA cases

Study	Number of SMA cases	Number symptomatic	*SMN2* copy number of symptomatic cases
Time point: First clinical visit			
Abiusi 2022[126]	15	6	• One *SMN2* copy (n =1) • Two *SMN2* copies (n = 5)
Elkins 2022[134]	15	6	• One *SMN2* copy (n = 2) • Two *SMN2* copies (n= 3) • Three *SMN2* copies (n=1)
Hale 2021[135]	9	6	• Two *SMN2* copies (n = 5) • Four *SMN2* copies (n = 1)
Kucera 2021[142]	1	1	• Two copies *SMN2* (n = 1)
Total	40	19	• One *SMN2* copy (n = 3) • Two *SMN2* copies (n= 14) • Three *SMN2* copies (n=1) • Four *SMN2* copies (n = 1)
Time point: Diagnosis			
Gailite 2022[69]	2	1	• Reported as type 0 (n =1)
Noguchi 2022[147]	2	1	• Two *SMN2* copies (n = 1)
Sawada 2022[148]	1	0	• NA
Kernohan 2021[139]	5	0	• NA
Kraszewski et al 2018[141]	1	0	• NA
Total	11	2	• Type 0 (n = 1) • Two *SMN2* copies (n = 1)
Time point: First four weeks of life			
D'Silva 2022[81, 136]	21	6	• NR
Vill 2021[132, 140, 146, 149-151]	43	8	• Two *SMN2* copies (n = 8)
Weng 2021[131, 152]	20	8*	• Two *SMN2* copies (n=8)
Total	84	22	• Two *SMN2* copies (n = 16) • NR (n = 6)
Time point: Treatment initiation			
Boemer 2021[52, 128, 129]	9	4	• Two *SMN2* copies (n = 4)
Lee 2022[138, 143]	34	9	• One *SMN2* copy (n = 1) • Two *SMN2* copies (n = 8)
Matteson 2022[145]	34	12	• Two *SMN2* copies (n = 8) • Three *SMN2* copies (n = 3) • Four *SMN2* copies (n = 1)
Kernohan 2021[47, 139]	5	0	NA
Kraszewski et al 2018[141]	1	0	NA
Total	83	25	• One *SMN2* copy (n = 1) • Two *SMN2* copies (n = 20) • Three *SMN2* copies (n = 3) • Four *SMN2* copies (n = 1)

Key: NA – non-applicable; NR – not reported; *SMN2* – survival motor neuron 2 gene.
* Five of these newborns were noted to have symptoms at birth.

Family history

Five studies provided details of the family history of identified cases with all but one of these studies being US-based.[135, 142, 143, 145, 151] The Massachusetts study reported that of nine cases detected through newborn bloodspot screening, one case had already been identified through prior prenatal testing, three cases had known parent carriers, and one case had one known parent carrier while the second parent had not been tested.[135] The North Carolina study reported that the single SMA case identified through newborn bloodspot screening had known parent carriers and had undergone prenatal testing which had highlighted a decreased risk for SMA.[142] The Californian study reported that 13 of 34 cases had a positive family history defined as a sibling previously diagnosed or known parent carriers.[145] The New York study reported that three out of 34 cases identified through screening had a prenatally known risk from a parental carrier status or family history of affected siblings.[143] Lastly, a German study reported that three out 43 cases had a positive family history, but did not specify if this was due to carrier status or siblings affected, and an additional 10 cases were considered to be at increased risk due to consanguinity.[151]

Cascade testing

Two studies reported the identification of siblings with SMA through cascade testing of family members of detected cases in newborn bloodspot screening programmes.[52, 151] The Belgian study reported that two asymptomatic siblings of one infant with four copies of *SMN2* were identified as having a homozygous deletion in *SMN1* and four copies of *SMN2*.[52] One became symptomatic at seven years, the other remained asymptomatic at publication of the study at the age of five years six months. The second study, completed in Germany, reported two cases of SMA, both with four *SMN2* copies, who had siblings subsequently diagnosed.[151] The respective five and six year old brothers of the infants both had unclear motor symptoms (from approximately three years of age). The former had been diagnosed as having congenital ataxia and the latter as displaying 'clumsiness'. A homozygous deletion in the *SMN1* gene was identified in both and a clinical diagnosis of SMA type III was made.

4.3.7 Outcome: Pathway timings

Pathway timings reported by studies included laboratory turnaround times, age at diagnosis, age at first clinical visit, and age at treatment. Laboratory turnaround times are outlined in Appendix Chapter 4, Table A4.4 with the remaining measures outlined by study type below.

4.3.7.1 Non-comparative studies

Age at diagnosis or first clinical visit

As outlined in Table 4.7, seven studies reported age at diagnosis for SMA cases identified through screening,[81, 126, 145, 147, 148, 151, 156] and five studies reported age at first clinical visit.[52, 134, 135, 141, 143] Excluding those studies with two or less cases of SMA, the median age at diagnosis ranged from six days[126] to 19 days,[156] and the median age at first clinical visit ranged from seven days[135] to 33 days.[134]

Table 4.7 Median age at diagnosis or first clinical visit

Study	Median age
Diagnosis	
Abiusi 2022[126]	6 days (range 5 to 9)
D'Silva 2022[81, 136]	15 days (range 10 to 23)
Kernohan 2021*[139, 156]	19 days (range 11 to 28)
Noguchi 2022[147]	Patient 1 diagnosed: 24 days Patient 2 diagnosed: 21 days
Matteson 2022[145]	12 days (range 0 to 54)
Sawada 2022[148]	Single patient diagnosed at 19 days
Vill 2021[132, 140, 146, 149-151]	14 days (range 9 to 23)
First clinical visit	
Boemer 2021[52, 128, 129]	21 days (range 10 to 37)
Elkins 2022[134]	33 days (range 15 to 46 days)
Hale 2021[135]	7 days (range 0 to 16)
Kraszewski et al 2018[141]	Single patient: 7 days
Lee 2022[138, 143]	9 days (range 1 to 58)

* Includes unpublished data provided by study authors.

Age at treatment

As outlined in Table 4.8, 14 studies reported age at treatment.[52, 81, 126, 127, 134, 135, 139, 141-143, 145, 147, 148, 151] Excluding those with two or less cases of SMA, the median age at treatment reported across the included studies ranged from 16.5 days[126] to 106 days.[134] To note, these values, and the associated ranges within each individual study, were likely impacted by the treatment pathways in the local context (for example, pre-symptomatic treatment versus treatment at onset of symptoms).

Table 4.8 Median age at treatment initiation

Study	Median age at treatment initiation
Abiusi 2022[126]	16.5 days (range 7 to 21)
Baker 2022[127]	18.5 days (range 11 to 57)
Boemer 2021[52, 128, 129]	38 days (range 29 to 54)
D'Silva 2022[81, 136]	25 days (range 15 to 39)
Elkins 2022[134]	106 days (range 28 to 189)
Hale 2021[135]	18 days (range 8 to 171)
Kernohan 2021*[139, 156]	21.9 days of age (range 18 to 39)
Kraszewski et al 2018[141]	Single patient: 15 days
Kucera 2021[142]	Single patient: 30 days
Lee 2022[138, 143]	34.5 days (range 11 to 197)
Matteson 2022[145]	33 days (range 17 to 79)
Noguchi 2022[147]	Patient 1: 25 days Patient 2: 22 days
Sawada 2022[148]	Single patient: 42 days
Vill 2021[132, 140, 146, 149-151]	21 days (range 14 to 300)

* Includes unpublished data provided by study authors.

4.3.7.2 Comparative studies

Pathway timings were presented for one of the three comparative studies as outlined in Table 4.9. As shown, this study from Australia,[137] which represents a subset of a population from a non-comparative study described above,[81] provided statistical comparisons of ages between groups. The results indicate a significant difference in age between the screening and comparator group ($p < 0.01$) for symptom onset, diagnosis, and treatment initiation, with all occurring at a younger age in the screening group.

Table 4.9 Pathway timings for comparative studies

Study	Time point	Median age (weeks) - screened	Median age (weeks) - unscreened	Statistical difference reported by authors
Kariyawasam 2023[153]	Symptom onset	2.9 (IQR 1.9 to 3.7)	21.4 (IQR 7.9 to 48.2)	p = 0.0086
	Diagnosis	2.1 (IQR 1.9 to 2.7)	47.8 (IQR 13.0 to 99.9)	p = 0.0003
	Treatment initiation	3.9 (IQR 2.7 to 5.1)	49.9 (IQR 123.9 to 145.6)	p = 0.0015

Key: IQR – interquartile range.

4.3.8 Outcome: Incidence

Thirteen of the included studies with at least 12 months of screening data provided estimates of SMA incidence on the basis of newborn bloodspot screening. The estimated incidence, and any comparison with previously reported incidence, presented by the study authors are outlined in Table 4.10. As shown, the incidence

varied widely across studies ranging from 1 in 6,059 in a pilot study in Italy to 1 in 19,000 in a population-level study in New York State.[143] The midpoint of all incidences reported was approximately 1 in 13,500. Considering the total number of SMA cases detected (n = 232) and the total number of infants screened (n = 3,381,079) in these studies, a collective incidence of 1 in 14,574 is estimated. As highlighted in the table, a number of authors provided comparisons to previously reported incidence rates; however, these are considered to be of limited value given that most related to general, as opposed to location-specific, incidence rates, and given the limited duration of screening and the regional implementation reported in a number of the included studies.

Table 4.10 Incidence of SMA reported across included studies

Study	Country (Region)	Estimated incidence as reported by study	Previous estimate of incidence
Abiusi 2022[126]	Italy (Lazio and Tuscany)	1 in 6,059	Other SMA programmes (range 1 in 5,206 to 1 in 28,137) and notes to be one of the highest reported thus far
Baker 2022[127]	US (Wisconsin)	1 in 10,164	1 in 11,000 from a US based estimation from carrier frequency
Boemer 2021[52, 128, 129]	Belgium (Southern region)	1 in 13,634 (95% CI: 1 in 8,417 to 1 in 35,858)	NR^
D'Silva 2022[81, 136]	Australia (New South Wales and the Australian Capital Territory)	1 in 11,458	NR
Elkins 2022[134]	US (Georgia)	1 in 18,840	1 in 6,000 to 11,000 (reference not provided)
Hale 2021[135]	US (Massachusetts)	1 in 18,957 (95% CI: 1 in 12,061 to 1 in 57,519)	1 in 12,000 from a 2017 literature review of SMA incidence
Kernohan 2021[139, 156]	Canada (Ontario)	1 in 16,429	NR
Kucera 2021[142]	US (North Carolina)	1 in 12,065	NR
Lee 2022[138, 143]	US (New York)*	1 in 19,000*	1 in 6,000 to 11,000 from a 1991 global survey of neuromuscular disorders
Matteson 2022[145]	US (California)	1 in 18,494 (95% CI: 1 in 13,841 to 1 in 27,858)	1 in 10,000 (reference not reported)
Sawada 2022[148]	Japan (Kumamoto Prefecture)	1 in 13,587	1 in 19,600 (95% CI: 1 in 14,100 to 1 in 31,300) from a 2022 Japanese estimate
Vill 2021[132, 140, 146, 149-151]	Germany (Bavaria and North Rhine-Westphalia)	1 in 6,910	1 in 7,352 from estimate for 2014 in Germany**
Weng 2021[131, 152]	Taiwan (One centre)	1 in 17,000 (95% CI: 1 in 11, 350 to 1 in 26,530)	NR

Key: CI – confidence interval; NA – non-applicable; NR – not reported; SMA – spinal muscular atrophy.
^ Assessed probability of cases of being detected over three years using Poisson distribution - estimated at 8.99 cases over three years with 9 cases observed.
* Incidence rate reported for initial 12 month pilot in same location with weekday recruitment at three hospitals by Krasewski et al. reported as 1 in 3,826 with one case detected.
** Previous incidence reported from 2014 in Germany and was the highest incidence reported over 23 years with the range being 1 in 7,352 to 1 in 37,037 with the incidence over time being approximately 1 in 13,000 (Konig et al).

4.3.9 Outcome: Clinical outcomes

Clinical outcomes were extracted from comparative studies only. Three studies in this systematic review were considered to be comparative in nature where the outcomes of screened and unscreened infants were presented.[130, 133, 137] As previously highlighted, only the study (from Australia) aimed to investigate the effectiveness of newborn bloodspot screening for SMA.[137] It is important to note that this study initially included a screen positivity threshold but later was amended such that all patients with homozygous deletion were identified.[155] Only one case with four copies was included in the screening cohort of this study. [153] Of the remaining two studies, one provided quality of life results for those not identified by symptoms (family history or newborn bloodspot screening) and those identified by symptoms but did not formally compare the results,[133] and the second study performed regression analyses of clinical outcomes with newborn bloodspot screening included as a variable of interest.[130] The outcomes of interest are outlined in Table 4.11.

Mortality

Only the non-randomised study from Australia presented any detail on mortality.[137] Three infants died over the course of the study period with one being from the screened group and two from the unscreened group; all three infants had two *SMN2* copies and had entered palliative care pathways without disease-modifying treatment.

Morbidity

Functional ability

The non-randomised study from Australia presented multiple measures of functional ability between the screened and unscreened groups.[137] At two years follow-up, significantly more children in the screened group were able to walk independently or with assistance compared with the unscreened group (11 versus 1, $p < 0.001$). Similarly, HINE-II scores (a composite measure of clinical milestones) were significantly higher, indicating better functional ability, in the screened group

compared to the unscreened group (p = 0.0013). Additionally, the authors noted a significant difference in HINE-II scores depending on the symptom status of the screened group at treatment initiation with those who were asymptomatic having higher scores than those who were symptomatic (p = 0.02) at two years follow-up. While Functional Independence Measure for Children (WeeFIM) scores (a measure of functional independence) were higher (suggesting greater functional independence) for the screened group, the results were not statistically different from the unscreened group. However, the study authors highlighted that the screened group were significantly younger than the unscreened group.

Ventilation and nutritional support

The authors of the Australian study noted that one child in the screening group required nutritional support and one required ventilator support compared with six children each in the unscreened group.[137] The authors highlighted that the need for nutritional and ventilator support remained stable over the study period in the screened group, while the number of children requiring support increased in the unscreened group.

Quality of life

The study from Belgium, Germany and France presented results of quality of life assessments using validated generic quality of life assessment tools.[133] As shown in Table 4.11 the sample size was very small for those not identified by symptoms (that is, those identified by newborn bloodspot screening and family history) and varied in the number of outcome measures completed. The authors did not provide formal comparisons, but noted that quality of life measures tended to be higher in those not identified by symptoms (all of whom were treated) compared with treated and untreated patients identified on the basis of symptomatic presentation. The exception was a subscale measure of family impact which was similar across all groups.

Table 4.11 Comparisons of clinical outcomes across groups

Study	Outcome	Measure	Screening group	Unscreened group	Statistical difference reported by authors
Kariyawasam 2023[137]	Survival at two years post diagnosis	Number alive	14 (93%)*	16 (89%)*	NR
	Morbidity at two years post diagnosis	Walking independently or with assistance	11 (79%)	1 (6%)	p < 0.0001
		HINE-II score	23.0 (SD 4.2)	15.1 (SD 6.7)	p = 0.0013 Group difference after adjusting for baseline: 12.3 (95% CI: 9.5 to 16.2)
		WeeFIM score	70.1 (SD 23.1)	60.6 (SD 31.8)	p = 0.38**
		Non-invasive ventilation	1 (7%)^	6 (38%)^	Odds ratio for requirement of ventilation or nutritional support: 7.1 (95% CI: 0.7 to 70.2)
		Nutritional support	1 (7%)^	6 (38%)^	
Dangouloff 2022[133]	Quality of life~	PedsQL	Not identified by symptoms:¥ ▪ Family impact: 62 (n = 13) ▪ GCS: 93 (n = 4) ▪ NMM: 86 (n = 4)	Treated symptomatic patients: ▪ Family impact: 57 (n = 32) ▪ GCS: 51 (n = 36) ▪ NMM: 62 (n = 36) Untreated symptomatic patients:	NR

				▪ Family impact: 51 (n = 4) ▪ GCS: 54 (n = 91) ▪ NMM: 66 (n = 90)	
		HUI	Not identified by symptoms:¥ ▪ HUI2: 1 (n = 3) ▪ HUI3: 1 (n = 3)	Treated symptomatic patients: ▪ HUI2: 0.52 (n = 35) ▪ HUI3: 0.26 (n = 35) Untreated symptomatic patients: ▪ HUI2: 0.54 (n = 91) ▪ HUI3: 0.28 (n = 91)	

Key: CI – confidence interval; GCS – Generic Core Scale; HINE - Hammersmith Infant Neurological Examination; HUI – Health Utility Index; NMM – neuromuscular model; NR – not reported; PedsQL - Pediatric Quality of Life Inventory; SD - standard deviation; WeeFIM – Functional Independence Measure for Children.

* The three children who died (one in screening group and two in unscreened group) all had two *SMN2* copies and entered palliative care pathway.

** Not adjusted by age with the screening group mean age being significantly younger than the comparator group.

^ Screening group stable from baseline, increased in comparator group.

¥ Includes those identified by screening and family history.

~ Results of the EQ-5D were also provided by study authors, but have not been included in the current review as only one patient not identified by symptoms was presented.

Associations with clinical outcomes

As outlined in Table 4.12, two studies presented additional analyses of associations with clinical outcomes.[130, 137]

The study from Australia presented results for correlation between age at diagnosis and motor function, and age at treatment and motor function.[153] Motor function, as assessed by Hammersmith Infant Neurological Examination-II (HINE-II) scores and World Health Organization (WHO) motor milestones, were not significantly correlated with age at diagnosis in either the screening or comparator group. However, in the screening group only, both scores were significantly associated with age at treatment ($p = 0.009$ and $p = 0.02$; respectively). Interpretation of these results is limited by the small number of cases ($n = 33$) and for the screened cohort, the limited variability in the age at diagnosis (all diagnosed by 22 days) and time to treatment (all treated by 39 days).

The study from the Asia-Pacific region presented results of a linear regression model.[130] Variables included identification of cases of SMA by newborn bloodspot screening, disease duration, *SMN2* copy number, and baseline functional outcome measure scores. In a univariate regression model for changes in motor milestone scores from pre-treatment to 10 months post-treatment, HINE-II scores were positively associated (indicating better outcomes) with identification based on newborn bloodspot screening ($p = 0.001$). Changes in HINE-II scores were also positively associated with baseline HINE-II scores ($p = 0.033$) and negatively correlated with disease duration ($p = 0.027$). In the multivariate regression model, only identification by newborn bloodspot screening was found to be significantly associated with positive increases in HINE-II scores ($p=0.009$).

Table 4.12 Additional analyses presented by studies

Study	Number included in analysis	Analysis	Results
Kariyawasam 2023[137]	Screened: n = 13 Unscreened: n = 14	Correlation between motor function and age at diagnosis	Screening cohort: ▪ HINE-II scores: r = 0.08, p = 0.79 ▪ WHO motor milestone: r = 0.25, p = 0.63 Comparator: ▪ HINE-II scores: r = - 0.37, p = 0.18 ▪ WHO motor milestone: r = -0.22; p = 0.41
	Screened: n = 12 Unscreened: n = 14	Correlation between motor function and age at treatment	Screening: ▪ HINE-II scores: r = 0.74, p = 0.009 ▪ WHO motor milestone: r = 0.67, p = 0.02 Comparator: ▪ HINE-II scores: r = -0.41, p = 0.13 ▪ WHO motor milestone: r = -0.17, p = 0.54
	Symptomatic: n = 5 Asymptomatic: n = 7	Difference in HINE-II scores by symptom status in screening group	Symptomatic (mean =17.0, SD = 3.7) versus asymptomatic (mean = 21.7, SD = 1.9) at treatment initiation (p = 0.02)
Chan 2021[130]	Screened: n = 9 Unscreened: n = 31	Changes in pre-treatment scores to 10 months post-treatment scores	Univariate regression: ▪ HINE-II: positively correlated with screening (p = 0.001) ▪ CHOP-INTEND: no significant correlation with screening Multivariate regression:* ▪ HINE-II: positively correlated with newborn bloodspot screening; p = 0.009 ▪ CHOP-INTEND: no significant correlation with screening

Key: CHOP-INTEND - Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; HINE - Hammersmith Infant Neurological Examination; WHO – World Health Organisation

* Adjusted for disease duration, *SMN2* copy number, and baseline scores with no other variable being significant.

4.3.10 Outcome: Potential harms of screening

A number of factors outlined within the included studies were noted by the HIQA evaluation team as suggestive of potential harms of newborn bloodspot screening for SMA.

Compound heterozygous variants

While not the target of screening within the included studies, ten studies emphasised that cases of SMA associated with compound heterozygous variants of *SMN1* would not be detected through screening (that is, deletion on one allele with point mutations of the other).[52, 81, 134, 143-145, 147, 148, 151] Two such cases were documented as being clinically identified over the study period in two studies.[52, 152] One study highlighted the need for clarity regarding this test limitation during the informed consent process for newborn bloodspot screening.[144]

Cases with higher *SMN2* copy numbers

Two of the 20 studies, included cut-offs for screen positives based on *SMN2* copy number, using a cut-off of three,[81] and four copies,[139] respectively. The first study, from Australia (New South Wales), cited the rationale for this cut-off as their perception of the clinical uncertainty (in terms of the potential for a long latent phase and cases presenting clinically in late childhood or as adults), alongside the fact that the policy was to not reimburse disease-modifying treatment for pre-symptomatic cases in Australia at the time of the study.[81] However, as noted above, at a later date they amended the program to remove this cut off.[155] In the second study, from Ontario, the authors considered that the natural history of infants with five or more *SMN2* copies is not wholly predictable, and adult onset or potentially remaining completely asymptomatic throughout life are possible outcomes.[47, 139] The authors concluded that reporting this condition when there is a chance that disease manifestation may not occur was unethical and may not be in patients' best interest in the Canadian setting given the potential psychosocial impact, exclusion from insurability, and other potential ramifications associated with this disclosure.

A third study, from Germany, also highlighted that newborn bloodspot screening may detect cases that would not otherwise present until adulthood. The authors outlined that employing a "watchful waiting" strategy for those with four or more copies of *SMN2* is typically based on the rationale that it avoids unnecessary, potentially harmful treatment for a number of children who might remain asymptomatic if untreated.[151] The authors of this study argued that if this is the case, the incidence rates following newborn bloodspot screening should be much higher than the incidence known in the general population. The authors further highlighted the balance in the burden of early treatment in a potentially late-onset

disease versus the risk of delayed diagnosis and treatment with irreversible motor damage in others. Three close relatives with the same genotype of patients with SMA with four *SMN2* copies detected through newborn bloodspot screening had developed SMA type III in early childhood which the authors argued further emphasised this uncertainty in relation to potential clinical outcome.

Parent and family impact

An Australian study highlighted the need for dedicated psychosocial input for families at a time of significant stress.[81] Additionally, as the treatment pathway and counselling are reliant on *SMN2* copy number in mostly pre-symptomatic infants this introduces uncertainties in conversations with parents about clinical severity and long-term outcomes.

Two studies noted parental hesitation in relation to treatment options with initial refusal of treatment in two cases identified as the children were asymptomatic with parental preference expressed to wait until symptoms presented.[52, 147] In both cases, the parents were counselled and subsequently accepted treatment recommendations. In one case in Germany, the family of a child with four *SMN2* copies dropped out of follow up after their 13-month check-up, when the child had learned to walk independently (having not received disease-modifying treatment).[151] The reason for this was the parent's extreme psychological stress that preceded the medical appointments.

4.3.11 Outcome: Acceptability of screening

Four studies were opt-out programmes,[52, 81, 127, 145] with one highlighting that the addition of SMA had not impacted the high uptake rate of the newborn bloodspot screening programme generally.[81] One US study that required specific consent for SMA screening separate to newborn bloodspot screening generally noted lower rates of uptake compared with previous state-wide implementations (85% versus 98%).[135]

Uptake rates were reported by four further pilot studies. An uptake rate of 87% was reported by authors in German regions.[151] A 91% uptake was reported during the pilot study period in Italian regions with uptake following subsequent regional implementation increasing to 98-99%, which the authors highlight as likely due to two reasons: informed consent form was simplified, and participating in a pilot study may have negatively influenced the parental choice.[126] A pilot study in New York noted 93% uptake ,with the most common reasons for declining to participate being general distrust of the healthcare system and prior poor experience with healthcare.[141] A Japanese pilot in the Hyogo Prefecture was associated with a 22% uptake rate and the authors hypothesised that willingness to participate may have

been impacted by parents' lack of awareness of the seriousness of the condition and the availability of pre-symptomatic treatment options.[147]

4.3.12 Quality appraisal of studies identified

As noted in the methodology section above, no formal quality appraisal tool was identified that was considered appropriate to the types of studies included in this systematic review. As such, *de novo* checklists were developed for each study type.

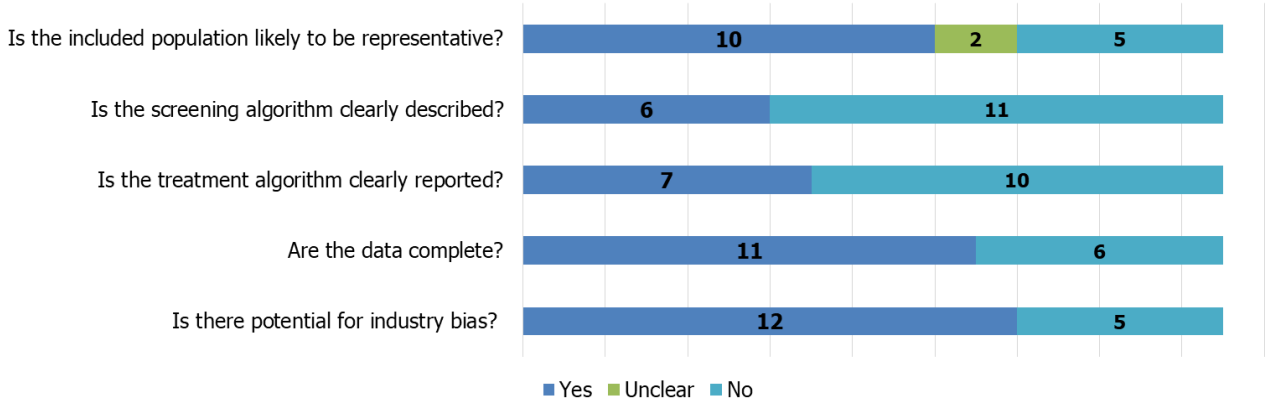
Non-comparative studies

The de-novo checklist for the 17 non-comparative studies included in this review considered the following areas:

- representativeness of the population
- description of screening algorithm
- description of treatment algorithm
- completeness of findings
- potential for bias.

Ten studies were considered to include a representative population.[52, 81, 126, 127, 134, 135, 139, 143, 145, 148] Of the remaining studies, limitations were noted including low uptake rates of screening, restrictive participant exclusion criteria, and lack of clarity as to the population offered screening.[69, 141-143, 147, 151, 152] Six studies were considered to provide an adequate description of the screening algorithm.[52, 69, 81, 126, 139, 145] The remaining 11 studies were unclear in relation to one or more aspects of their screening algorithm.[127, 134, 135, 141-144, 147, 148, 151, 152] Concerning the treatment algorithm, seven of the included studies outlined both the treatments available as well as detailing the treatment criteria,[69, 81, 135, 139, 144, 151, 152] while the remaining studies failed to clearly outline decision-making criteria relating to treatment.[52, 126, 127, 134, 141-143, 145, 147, 148] Regarding completeness of reporting, 11 studies were considered to provide complete data,[52, 81, 126, 134, 135, 139, 141, 145, 148, 151, 152] with reporting limitations noted in the remaining six studies as to data relating to pathway timings,[69, 127, 142-144, 147] SMA case characteristics, and the potential for missing data. Five studies did not raise concern of the potential for industry bias; these were primarily carried out by national and or public health organisations.[69, 134, 135, 145, 148] The remaining studies (n = 12) demonstrated potential bias through factors such as industry funding, industry employment, advisory and consultancy positions.[52, 81, 126, 127, 139, 141-144, 147, 151, 152] Links to SMA advocacy groups through research funding were noted in two studies.[127, 142]

Figure 4.1 Quality checklist for non-comparative studies



Comparative studies

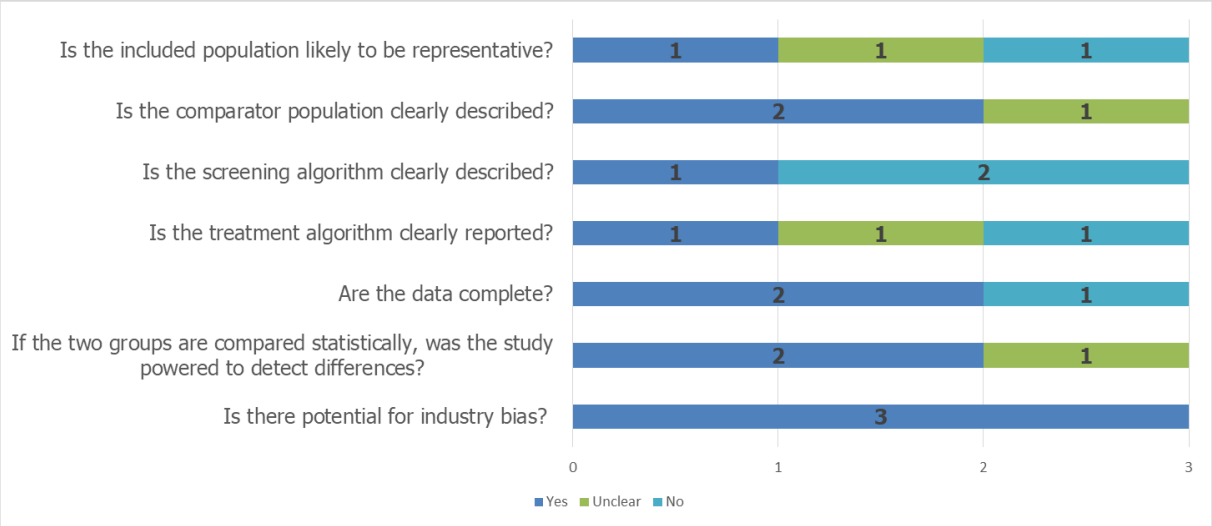
The de-novo checklist for the three comparative studies included in this review considered the following areas:

- representativeness of the screened population
- representativeness of the comparator population
- description of screening algorithm
- description of treatment algorithm
- completeness of findings
- statistical comparisons
- potential for bias.

It should be noted that while the aim of this review was to assess the effectiveness of screening, this was not necessarily the aim of the included studies (that is, they contained data of relevance to the review question, but may not have set out to consider effectiveness of screening explicitly). Therefore, the results of the quality assessment below reflect the ability of the study to answer the review question rather than the explicit quality of the study itself. One study was considered to include a representative population.[137] The remaining two studies, were considered to have limitations including unclear uptake rates of screening, restrictive participant exclusion criteria, and or lack of clarity in relation to the population offered screening.[130, 133] Two studies clearly described and reported a representative comparator population.[133, 137] Only one study was considered to have clearly described a screening algorithm, albeit this was reported in a separate publication.[137] Concerning the treatment algorithm, again just one of the included studies clearly outlined the algorithm used.[137] Regarding completeness of reporting, two studies were considered to provide complete data.[133, 137] In the remaining study, limitations were noted in terms of data missing cases, baseline and outcome data.[130] One study outlined that the analysis was powered to detect differences

between groups.[137] All three studies raised the concern of the potential for industry bias through factors such as industry funding, industry employment, advisory and consultancy positions. While associated with limitations, this evidence-base represents the best available at the current time.

Figure 4.2 Quality checklist for comparative studies



4.4 Discussion

The aim of this chapter was to describe the clinical effectiveness of newborn bloodspot screening for SMA. This aim was facilitated through a systematic review of the international literature of approaches and outcomes of newborn bloodspot screening for SMA. For the purposes of this HTA, the term 'clinical effectiveness' encompasses the NSAC criteria of the screening method and the screening programme. Accordingly, this systematic review sought to summarise the approaches used by newborn bloodspot screening programmes for SMA internationally and the outcomes of these programmes. Seventeen of the 20 included studies were non-comparative and provided details relating to approaches used and outcomes such as test performance, case characteristics, screening pathway timings, incidence of SMA, and potential harms of this form of screening. While a number of these studies further provided clinical outcome data for cases of SMA identified through screening, these data were not compared to unscreened cohorts, hence the studies provide limited information on the effectiveness of screening specifically. Three studies were identified which provided detail of clinical outcomes for screened and unscreened cohorts.

With regards to the approaches used for newborn bloodspot screening, the included studies were notably heterogeneous in terms of the screening algorithms and test methodologies used. As with previous assessments of newborn bloodspot screening, it is noted that the establishment and validation of the algorithm and methodology will be required at the local level prior to the implementation of a newborn bloodspot

screening programme for SMA.[10, 157] The included studies all cited homozygous deletions in *SMN1* as the primary target of screening, with variation in the number of screening test tiers and targets thereafter. Half of the included studies used a single tier testing method with positive screens being referred directly for confirmatory testing, with the other half including a second tier which enabled confirmation of *SMN1* deletions and or quantification of *SMN2* copy number. Where *SMN2* copy number was assessed in the second tier, a number of studies highlighted the clinical benefit of identifying those at potentially higher risk of severe clinical disease and enabling counselling on treatment options to begin at the first clinical visit while awaiting confirmatory testing results.[52, 81, 127, 143] Two studies within this review further included a cut-off for screen positives specifically related to *SMN2* copy number with the rationale provided centring on the uncertainty of clinical course in those with higher *SMN2* copy numbers.[81, 139] However, one of the studies subsequently removed this threshold during the course of the pilot.[155] In this way, while meeting the criteria for SMA in terms of bi-allelic disruption in *SMN1*,[1] a decision to not inform families or caregivers of this finding was based on clinical uncertainty in prognosis. This uncertainty in clinical course was further highlighted as impacting the parents and family of SMA cases during decision-making on treatment options. As noted, the prognostic accuracy of *SMN2* copy number is not absolute and this factor pervades this HTA. This element has implications on both sides where the use of a threshold for treatment may result in severe cases with higher copy numbers not receiving early intervention while cases with a lower copy number, who would not subsequently develop a severe form, will receive a treatment not otherwise indicated. The influence of this uncertainty in terms of screening algorithms and ethical considerations are further be explored in chapters 3 (epidemiology) and 8 (ethical and social considerations).

Despite being heterogeneous in approach, the majority of studies presented PPVs at or above 90% with correspondingly low false positivity rates as a percentage of those referred for confirmatory testing. There were two notable exceptions to this.[134, 147] Neither of these studies included a second tier test; however, the lack of a second tier test did not equate to a high false positivity rates in other studies included in this review. One study highlighted that the cut-off used may have been too conservative and both studies cited the potential impact of samples being collected from acutely unwell children in specialist care settings. Such factors have been documented as affecting newborn bloodspot screening accuracy and guidance from the UK cites the importance of avoiding contamination when collecting such samples (for example, heparinised capillary tubes impact on DNA testing).[158] Across the studies, as a percentage of the population screened, the false positivity rate reported was less than 0.01% (< 1 in 10,000 screened) in all but one study (0.12%). Considering an annual birth cohort of approximately 58,000 in Ireland, this would equate to up to 75 false positive screening tests per year; however, this upper

bound reflects outlier studies in the context of this review, with the number of false positives equating to fewer than six screening tests per year if the false positivity rate reported in the majority of studies is used. With respect to consideration of the potential harms of screening, it is noteworthy that it may be possible to perform confirmatory testing on the original bloodspot sample taken for the purpose of newborn screening. If this is the case, this would mean that there would be no need to contact the family for a separate blood draw, thereby minimising the impact of a false positive screening result on them. Decisions on sample requirements (blood spot or a separate venous blood draw) would be taken at the laboratory verification stage prior to implementation.[25]

Given the nature of the studies included, limited information was presented with regards to undetected cases; however, previous analytical studies have noted complete rates of detection of known SMA cases used as controls.[132, 159-161] A number of included studies outlined human and system errors resulting in samples not being tested or reported which, while not a limitation of the test specifically, reemphasises the importance of robust quality assurance processes for newborn bloodspot screening. As the target of this form of screening is homozygous deletions in *SMN1*, cases of SMA resulting from compound heterozygous variants (that is, deletion on one allele with point mutations of the others) will not be detected by this form of screening. While this does not necessarily represent a harm in the context of a defined screening test, it is important that this factor is clearly communicated during informed consent to ensure such cases presenting symptomatically are not overlooked on the basis of a previously negative screening result.[144] Additionally, while the rate of compound heterozygous variant causes of SMA are generally reported to be approximately 5%, it may differ across ethnic groups.[2, 3, 5] For example, the frequency may be higher thein black South Africans. This variation necessitates further caution when interpreting results in certain ethnicities.[162]

SMA is associated with progressive and irreversible destruction of the nerve cells in the brain and spinal cord. The main goal of screening programmes for SMA is to enable earlier diagnosis and treatment with a view to improving outcomes. For patients with up to three *SMN2* copies, a specific aim is to treat patients on diagnosis prior to them becoming symptomatic. However, even with a screening program, results from this review show that it was not always possible to meet this goal. Across various time points up to and including treatment initiation, 68 (32%) of 212 cases were reported by the included studies as being symptomatic with the majority of these having two *SMN2* copies. It is important to note that many of these results are in the context of pilot screening programmes and or where treatment was only available in the context of a clinical trial. It could be anticipated that the time from screening to treatment may be faster in fully implemented programs where screening and treatment pathways are established. Further, given

the anticipated increased recognition of SMA symptoms in patients who are known to have SMA compared to those who are not known to have the condition,[163] screening is still expected to reduce the time to diagnosis and treatment and thus potentially lead to improved outcomes. To note, in Ireland, the delay from diagnosis to treatment for symptomatic patients is reported to be seven to 14 days for cases of SMA.[26]

Carrier testing may further affect the value of screening. A number of US based studies highlighted cases of SMA born to known carrier parents, with preconception carrier screening recommended in the US for those with and without a family history of SMA (although it is unclear the extent to which this is standard practice).[32] Such infants may be considered high risk with the option of targeted screening through prenatal or neonatal testing means. In Ireland, carrier screening is typically only undertaken in the case of a positive family history.[26]

A limited number of additional cases of SMA were identified within the included studies through cascade testing of siblings. These cases included an asymptomatic child who subsequently presented with symptoms, two clinically misdiagnosed symptomatic cases, and a case who remained asymptomatic at the time of study completion. The identification of such cases may be associated with similar potential benefits and harms as those associated with the index case.

Typically cited incidence rates of SMA globally range from 1 in 10,000 to 1 in 12,000.[21] The reported incidence rates of SMA, associated with homozygous deletions, by the included studies varied widely (from 1 in 6,059 to 1 in 19,000) and none were considered to provide reliable comparisons to pre-screening rates. These studies are limited by short time periods of screening; longer durations would be required to accurately assess impact on incidence. The question as to whether newborn bloodspot screening results in an increase in incidence is an important one, but cannot be reliably answered by the data presented to date. It is plausible that, in the absence of screening, there are cases of SMA who remain asymptomatic or mildly symptomatic and do not present clinically. While a limited number of such cases have been reported in the literature, typically through carrier testing of family members of index cases, it is highly uncertain how frequent such occurrences are.[21, 88] Additionally, given the nature of SMA, it is inevitable that screening will detect cases in infancy who would not otherwise present until later in childhood or, in an anticipated minority of cases, into adulthood.

Limited data were identified from three studies within this review on the impact of newborn bloodspot screening on morbidity, with all three presenting a potential positive impact on such outcomes. One Australian study provided statistical comparisons of outcomes in a screened cohort (n = 15) versus an unscreened cohort (n = 18) with evidence to suggest improved functional outcomes with

screening, albeit in a small sample size.[137] This study further provided evidence to suggest that cases of SMA detected through screening and who initiate treatment when asymptomatic have improved outcomes compared with cases that are detected through screening, but who are symptomatic on treatment initiation. While providing promising results of the effect of newborn bloodspot screening on clinical outcomes, these studies were restricted to a maximum of two years of follow up data.

Since these results were complied, a systematic review of outcomes relating to patients with SMA identified through newborn blood spot screening was published (June 2023).[163] All studies included in the published review were also identified in this HTA, other than two studies that did not meet the inclusion criteria (they did not provide the outcomes of test performance, SMA case characteristics, incidence, or potential harms, and did not compare to unscreened cohorts).[164, 165] In contrast to the findings of the present review, which presented clinical outcome data only from comparative studies, the authors presented clinical outcome data relating to both comparative and non-comparative studies. Based on these data, the authors concluded that patients with three *SMN2* copies and no symptoms had an excellent functional prognosis. However, patients with two *SMN2* copies and symptoms at treatment initiation were still very likely to present with motor delay and ambulation cannot be guaranteed.

While the present review found limited data regarding the effectiveness of screening for SMA on clinical outcomes specifically, the data presented here represent the best available evidence at the current time. The effectiveness of screening interventions is inherently linked to the effectiveness of treatment which, as is outlined in chapter 5 (overview of treatments), are also currently associated with limited follow up data. It is important however, to not rely solely on results from clinical trials conducted in presymptomatic infants as these results may not be applicable to the whole population. In particular, outcomes for patients who become symptomatic before treatment are much less favourable than for those treated presymptomatically.[163] In the context of a rare disease, the recency of the implementation of population-based screening, and the recency of the availability of disease-modifying treatment with limited follow up data, it is likely that this evidence base will evolve in the short to medium term.

Limitations

The findings of this review should be interpreted in light of a number of limitations. As outlined, a degree of overlap and duplicate reporting across studies was identified. While a concerted effort has been made to only include unique populations within the present review, including contacting of authors, a risk remains that duplication could have occurred.

While a formal quality appraisal tool was not identified for the studies included in this review, a *de novo* checklist was created and piloted by the evaluation team to assess completeness of reporting relative to the design of each study. As highlighted within the quality appraisal section, a large number of the included studies were noted to have potential for industry or advocacy bias. While the effect of such bias cannot be fully determined, it should be considered as a potentially limiting factor in the interpretation of the available evidence.

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).

As per the protocol for this review, a decision was taken to only include clinical outcomes for studies considered to be comparative in nature (that is, where results for both screened and unscreened cohorts were presented). While clinical outcomes of single cohorts in non-comparative studies may provide additional insight in relation to early detection, they have not been summarised within this review. It was considered that these studies would reflect the effectiveness of treatment, as opposed to screening.

5 Overview of treatments

Key points

Overview of SMN-dependent drug treatments

- As of September 2023, three survival motor neuron (SMN) dependent drugs have been licensed by the European Medicines Agency (EMA) for the treatment of spinal muscular atrophy (SMA): nusinersen (Spinraza®), onasemnogene abeparvovec (Zolgensma®) and risdiplam (Evrysdi®). The drugs differ in their mechanisms of action, treatment duration, and administration schedules.
    - Both nusinersen and risdiplam may be administered for an indefinite duration provided the patient continues to benefit from treatment. Both drugs act to enhance the production of SMN protein from the survival motor neuron 2 (*SMN2)* gene. Nusinersen is administered via intrathecal injection (that is, into the area around the spinal cord) initially every 14 days, decreasing over time to administration every four months. Risdiplam is administered via oral solution daily.
    - Onasemnogene abeparvovec (OA) is a gene therapy which is administered as a one-off therapy via intravenous infusion. This treatment acts to replace the missing or non-functional survival motor neuron 1 (*SMN1)* gene.

Licensing and reimbursement in Ireland

- The drugs differ in their licensed indications and in their reimbursement by the HSE (that is, availability within the publicly funded healthcare system). Managed access protocols have been introduced by the HSE and are overseen by the Medicines Management Programme.
    - These drugs are associated with very high drug acquisition costs. Annual costs to the HSE based on the list price were estimated as approximately €255,000 per patient for each of nusinersen and risdiplam and €2.2 million per patient for OA when administered as a one-off treatment. The actual costs to the HSE are anticipated to be lower, but this cannot be confirmed due to the confidential nature of the agreements.
    - The managed access protocols in place as of September 2023 outline criteria that must be met before nusinersen, OA or risdiplam can be reimbursed for an individual patient. These criteria differ depending on whether the patient is symptomatic or presymptomatic at treatment initiation.

- While treatments are available for SMA, reimbursement arrangements have not been agreed in the context of screening and would need to be clarified.

- For patients with **symptomatic disease**, as of September 2023:
  - No treatment is reimbursed for those with type 0 or type IV disease.
  - Nusinersen and risdiplam are reimbursed for those with type I, II or III disease and are limited to patients aged less than 18 years at treatment initiation.
  - OA is reimbursed for patients with type I disease.

- For **presymptomatic** patients, as of September 2023:
  - OA is reimbursed for patients with up to three *SMN2* copies; the upper age limit for reimbursement is unclear. The managed access protocol and the summary of product characteristics report that there is limited experience for those aged over two years.
  - The managed access protocols for nusinersen and risdiplam note that a clinical diagnosis of SMA (that is, presence of symptoms) is an eligibility criterion.

Treatment effectiveness

- Published interim efficacy data for **presymptomatic** treatment initiation were identified from three ongoing trials.
  - One trial each was identified for nusinersen (n = 25), OA (n = 29), risdiplam (n = 6) with follow-up ranging from 12 months to a median of 2.9 years.
  - The studies were all single-arm and reported findings are limited to individuals with two or three copies of *SMN2*.
  - Across the three trials, all patients were alive at follow up, with no patient requiring permanent mechanical ventilation. Functional outcome data indicated that the majority of children achieved their motor milestones within the normal development range.

- Efficacy data for **symptomatic** treatment initiation were identified from five trials that informed the EMA authorisation of the three drugs:
  - Two trials were identified for nusinersen (both randomised controlled trials (RCTs)), one trial for OA (single arm) and two ongoing trials for risdiplam (one single arm, one RCT).
  - Three trials (one each for nusinersen (n=122), risdiplam (n=17) and OA (n=22)) recruited participants with type I disease and up to two copies of *SMN2.* The two remaining studies, which examined risdiplam (n=180) and nusinersen (n=126) recruited participants with type II or III disease.

  - Reported follow-up ranged from six to 18 months.
  - Results published to date demonstrate motor and developmental improvements across studies. Data from the studies of nusinersen and OA in type I patients indicate improved event-free survival (that is, absence of death or permanent ventilation) compared to a control group and natural history cohort, respectively.

- No trials were identified that directly compared presymptomatic initiation of treatment to treatment once a patient with SMA has become symptomatic.
  - Evidence from a subgroup analyses of trials in the symptomatic setting suggests that early treatment with nusinersen may be associated with greater improvement compared with later treatment.
  - Unadjusted naïve comparisons of outcomes observed in clinical trials, for patients expected to develop type I SMA and who were treated with nusinersen or OA, suggest that presymptomatic treatment may lead to improved outcomes compared with symptomatic initiation. However, such comparisons are heavily prone to bias.

- While treatment related adverse events were reported, few serious safety concerns were identified in the clinical trials examined. Serious liver failure and acute liver failure (including two fatal cases) have been reported with OA post authorisation.

- Based on limited data there is evidence that these drugs lead to improved outcomes in symptomatic individuals relative to the natural history of the disease. Fewer data are available for presymptomatic patients, with some evidence of improvement for those with two or three copies of *SMN2*. The evidence (primarily in type I disease) also suggests that earlier treatment may be more beneficial than later treatment. Follow-up data are limited; therefore, there is substantial uncertainty regarding the long-term effectiveness of these treatments.

5.1 Introduction

One of the criteria of the National Screening Advisory Committee (NSAC) for appraising the viability, effectiveness and appropriateness of a screening programme is that there should be an effective intervention for patients identified through screening with evidence that intervention at a presymptomatic phase leads to better outcomes for the screened individual compared with usual care. As described in chapter 2, survival motor neuron (SMN)-dependent drugs (that is, forms of disease-modifying treatments which act to increase SMN levels) are an important potential treatment option for children with spinal muscular atrophy (SMA) who would be identified through the National Newborn Bloodspot Screening Programme (NNBSP). This chapter aims to describe SMN-dependent drug treatments for SMA and their effectiveness both in patients who are symptomatic at treatment onset and in those that initiate treatment prior to symptom onset.

Firstly, the methods used to inform this chapter are outlined. Secondly, characteristics of the treatments and their availability in Ireland are detailed. Considering effectiveness, trials of presymptomatic initiation of treatment are described, followed by a description of the trials of symptomatic initiation which were pivotal for European Medicines Agency (EMA) approval of these drugs. A summary is also provided of a systematic review identified in the literature which analysed real-world evidence for the effectiveness of these treatments. The chapter concludes with a discussion of the main findings.

5.2 Methods

Overview of drug treatments

To inform the overview of SMN-dependent drug treatments, key documents relating to the licensing and reimbursement of the medicines in Ireland were reviewed. Pharmaceutical characteristics and licensing information were primarily sourced from the Summary of Product Characteristics (SmPCs) documents for treatments approved by the EMA. Where supplementary information was required, additional documents in the peer reviewed literature and grey literature were sourced. Managed access protocols (MAPs) prepared by the HSE Medicines Management Programme (MMP) were reviewed to outline the status of these drugs in Ireland with respect to their reimbursement. Additional information and clarifications surrounding drug reimbursement were also acquired from correspondence with the MMP and the Corporate Pharmaceutical Unit (CPU) of the HSE.[166, 167]

Treatment effectiveness

As part of scoping work conducted to inform this HTA, it was identified that there are three relevant SMN-dependent treatments licensed by the EMA for SMA, the first

of which was licensed in 2017. An overview of treatment efficacy is provided by describing the findings of the key clinical trials informing drug authorisation.

Key (pivotal) trials that informed EMA authorisation of the three drugs were identified from the relevant European public assessment reports.[168] This list of trials was supplemented by a search of the website www.clinicaltrials.gov to identify trials examining presymptomatic initiation. A list of relevant trials identified from this search is reported in Appendix Table A5.1. A narrative summary was produced detailing the characteristics and outcomes for each of these trials. Of note, all pivotal trials for EMA authorisation described symptomatic initiation of the treatment as opposed to efficacy in presymptomatic initiation. No trials were found that directly compared presymptomatic initiation of the drugs to symptomatic initiation.

Scoping searches were carried out to identify existing systematic reviews of treatment effectiveness. A systematic review by Erdos et al., published in 2022, was identified as relevant to this HTA.[169] This review presented a narrative summary of published data for all three SMN-dependent therapies for SMA and their combinations in all SMA types; outcomes were reported for safety or effectiveness with at least 12-months follow-up. To assess the quality of the systematic review, the HIQA evaluation team completed the AMSTAR-2 checklist. The checklist was completed independently in duplicate, and conflicts were resolved by discussion (Appendix Table A5.2). While a number of limitations with the reporting of the review were identified, it was found to be comprehensive and given its recent publication, an update to the review was not considered necessary.

5.3 Overview of SMN dependent drug treatments

As of September 2023, three SMN-dependent drugs have been authorised by the EMA for use in the EU – nusinersen, onasemnogene abeparvovec (OA) and risdiplam.[29-31] All are designated as orphan medicines by the EMA. Orphan medicines are intended for the treatment of a condition that has a prevalence of less than 5 in 10,000, which is life threatening or chronically debilitating, and that has no satisfactory prevention or treatment. If a medicine to treat the condition already exists, then the orphan medicine should demonstrate a significant benefit over available treatment options to receive this designation.

Product characteristics including pharmaceutical properties, licensed indication, reimbursement criteria and cost are summarised in Table 5.1 and are described in further detail below.

Table 5.1 Characteristics and HSE reimbursement criteria of SMN-dependent drugs licensed for SMA+

Characteristics and HSE reimbursement criteria	Nusinersen (Spinraza®)	Onasemnogene abeparvovec (Zolgensma®)	Risdiplam (Evrysdi®)
EMA License	For the treatment of 5q Spinal Muscular Atrophy.[29]	Patients with 5q SMA with a bi-allelic mutation in the *SMN1* gene and: ▪ a clinical diagnosis of SMA type I or ▪ up to 3 copies of the *SMN2* gene[31]	For the treatment of 5q SMA in patients with ▪ a clinical diagnosis of SMA type I, type II, or type III or ▪ one to four copies of *SMN2*.[30, 170]
Pharmaceutical form and method of administration	Solution for intrathecal use by lumbar puncture. Each 5ml vial contains 12mg nusinersen.[29]	Solution for intravenous infusion. Each mL contains OA with a nominal concentration of 2×10^{13} vector genomes (vg).[31]	Powder for oral solution. After reconstitution, each 80ml bottle contains 60mg risdiplam (0.75mg /ml).[30]
Dose	Loading dose of 12mg (5ml), by intrathecal injection, on days 0, 14, 28 and 63, followed by a maintenance dose of 12mg (5ml) once every 4 months thereafter.[29]	Nominal dose of 1.1×10^{14} vg/kg [31]	The recommended daily dose is determined by age and body weight: ▪ <2 months of age: 0.15 mg/kg body weight ▪ 2 months to < 2 years of age: 0.2 mg/kg body weight ▪ ≥ 2 years of age and < 20 kg: 0.25 mg/kg body weight ▪ ≥ 2 years of age and ≥ 20 kg: 5mg (fixed).[30]
Treatment duration (per product license)	Indefinite[29]	One-time administration only[31]	Indefinite[30]

Characteristics and HSE reimbursement criteria	Nusinersen (Spinraza®)	Onasemnogene abeparvovec (Zolgensma®)	Risdiplam (Evrysdi®)
Estimated drug cost to the HSE (calculated based on list price)*	Annual cost per patient in year 1 €407,397 (€509,802 including VAT) Annual cost per patient after year 1*: €203,698 (€254,901 including VAT) [171, 172]	€1,759,447 per patient* (€2,201,713 including VAT)[171, 172]	For patients ≥ 2 years of age and ≥ 20 kg the annual cost per patient is calculated as €251,072 (No VAT payable).[171, 173] Lower annual costs would be observed for patients who are < 2 years of age or who weigh < 20kg.
Primary HSE reimbursement criteria#¥	**Under 18 years at initiation** Symptomatic Clinical diagnosis of diagnosis of 5q SMA type I, type II or type III at the time of application.[174] Selected exclusion criteria:# ▪ Patients where the clinical and genetic diagnosis of SMA is not fulfilled ▪ Patients with SMA type 0 or type IV ▪ Patients who have had successful treatment with OA. Presymptomatic[166] The managed access protocol states that a clinical diagnosis of SMA is an explicit eligibility criterion for treatment. **18 years and over at initiation** Not reimbursed.[174]	▪ Confirmed diagnosis of 5q SMA with a bi-allelic mutation in the SMN1 gene and a clinical diagnosis of SMA type 1, or ▪ Confirmed diagnosis of presymptomatic 5q SMA with a bi-allelic mutation in the SMN1 gene and up to 3 copies of the *SMN2* gene. Additional criteria: [166] ▪ AAV9 titres of are required to be < 1:50 following re-testing[175] ▪ Upper age limit for reimbursement is unclear. The SmPC and the managed access protocol report that there is limited clinical experience in those aged over 2 years.	**Under 2 months at initiation** Not reimbursed. **[173]** **Aged between two months and 18 years at initiation[173]** Symptomatic Clinical diagnosis of diagnosis of 5q SMA type I, type II or type III at the time of application.[174] Selected exclusion criteria:# ▪ Patients where the clinical and genetic diagnosis of SMA is not fulfilled ▪ Patients with SMA type 0 or type IV ▪ Patients who have had successful treatment with OA. ▪ Patients who have had previous treatment with nusinersen who meet the discontinuation criteria for nusinersen.

Characteristics and HSE reimbursement criteria	Nusinersen (Spinraza®)	Onasemnogene abeparvovec (Zolgensma®)	Risdiplam (Evrysdi®)
			<u>Presymptomatic</u> The managed access protocol states that a clinical diagnosis of SMA is an explicit eligibility criterion for treatment. **18 years and over at initiation**[173] Not reimbursed.
Selected stopping rules under managed access protocol[#]	▪ Where one scale has been measured from baseline: discontinue if total worsening in scale score ○ > 2 points on horizontal kick or one point on other HINE scores (excluding voluntary grasp) ○ > 4 points on the CHOP-INTEND scale ○ > 3 points on the RHS ▪ Where two (or more) scales have been measured from baseline discontinue if there is total worsening in scale score(s), in the absence of any stability or improvement in other scales. ▪ In all cases, declines should be corroborated by two consecutive measurements (in order to allow for confirmation of worsening and not an 'off' assessment day).[174]	N/A	▪ Where one scale has been measured from baseline: discontinue if total worsening in scale score ○ > 2 points on horizontal kick or one point on other HINE scores (excluding voluntary grasp) ○ > 4 points on the CHOP-INTEND scale ○ > 3 points on the RHS ▪ Where two (or more) scales have been measured from baseline discontinue if there is total worsening in scale score(s), in the absence of any stability or improvement in other scales. ▪ In all cases, declines should be corroborated by two consecutive measurements (in order to allow for confirmation of worsening and not an 'off' assessment day).[173]

Key: AAV - adeno associated virus; CHOP-INTEND -The Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; HINE - Hammersmith Infant Neurological Examination; kg – kilogram; ml – millilitre; mg – milligram; N/A – not applicable; RHS- Revised Hammersmith Scale; SMA – spinal muscular atrophy; SMN – survival motor neuron; SmPC – Summary of product characteristics; OA - onasemnogene abeparvovec; vg - vector genomes.

* The net drug acquisition costs are anticipated to be lower than the publicly available list price (ex-factory price or reimbursement price), but this cannot be confirmed due to the confidential nature of the agreements.[167, 173-175] Drug costs were calculated in line with NCPE guidelines for the inclusion of drug costs in pharmacoeconomic evaluations and the NCPE budget impact model template. See chapter 7 (organisational and budgetary implications).[171, 176]
# The full list of exclusion criteria and stopping rules are available in the managed access protocols.[173-175]
+ As a screening programme for SMA is not in place in Ireland, to date, few presymptomatic patients have been identified for treatment. Reimbursement criteria were devised based on the existing mode of presentation of patients with SMA; that is, they do not take account of a potential screening programme for SMA.
¥Subsequent treatment with an alternative treatment is possible if there is a suboptimal response, where the patient still meets the eligibility criteria for those alternative treatments.

5.3.1 Pharmaceutical characteristics

Nusinersen

The first EMA-authorised drug treatment for SMA, nusinersen (Spinraza®) was approved for use in the EU for patients with 5q-SMA in 2017.[29] It is an antisense-oligonucleotide which enhances the inclusion of exon 7 in mRNA transcripts of survival motor neuron 2 *(SMN2)* by binding to an intronic splice-silencing-site in intron 7 of *SMN2*.[19] The result is an increased production of *SMN2*-mRNA with included exon 7, and therefore, more functional, full-length SMN protein. Nusinersen is given by intrathecal injection (that is, into the area around the spinal cord) as it is unable to pass the blood brain barrier when delivered systemically.[29, 177] Sedation may be required, and use of ultrasound-guided administration is sometimes used, particularly for younger patients and in patients with scoliosis.[29] Nusinersen is initially administered as a loading dose and then followed up as maintenance doses every four months thereafter. Treatment is indicated indefinitely.[29] In practice, if disease progression leads to severe scoliosis, this may reduce the ability to safely administer nusinersen and limit the treatment duration achieved.[26] Common adverse effects relating to the administration of nusinersen as described in the SmPC include meningitis, hypersensitivity, headache, vomiting and back pain.[29]

Onasemnogene abeparvovec

Onasemnogene abeparvovec (Zolgensma®), also known as OA, was authorised for use in the EU in 2020, and is intended for patients with SMA type I or patients with up to three or fewer copies of the *SMN2* gene.[31] OA is a gene therapy that aims to introduce a functional copy of the *SMN1* gene and therefore provide sustained SMN expression in motor neurons.[177, 178] It is administered as a one-off therapy via intravenous infusion. OA can cross the blood-brain barrier and enter neurons in the central nervous system (CNS).[31]

The gene is transported into the cells using the adeno-associated virus 9 (AAV9) vector. AAV9 is not known to cause disease in humans. However, following natural exposure to AAV9, anti-AAV9 antibodies can develop in patients; these antibodies are expected to neutralise the viral vector and reduce drug efficacy. While prior exposure to AAV9 in the paediatric population is thought to be low, patients should still be tested for the presence of AAV9 antibodies prior to treatment.[31] It is unknown whether OA can be safely administered if a patient's antibody titres are above 1:50. There is also limited experience with OA in patients two years of age and older or with a body weight above 13.5 kg.[31]

There is a risk of immune-mediated acute serious liver injury and acute liver failure with OA. To mitigate this risk, the SmPC includes recommendations surrounding systemic administration of corticosteroids, and close monitoring of liver function

before and after treatment with OA with a note that if immune-mediated hepatotoxicity occurs, further adjustment of the corticosteroid regimen may be indicated.[31] Of note, despite receipt of corticosteroids before and after infusion, two fatal cases of acute liver failure have been reported with OA.[31]

Other special warnings outlined in the SmPC, which mean that close monitoring is required before and after treatment, include risk of thrombocytopenia, thrombotic microangiopathy, elevated troponin, and systemic immune responses. Common adverse effects described in the SmPC include thrombocytopenia, vomiting, hepatotoxicity, pyrexia, increased hepatic enzymes, and increased troponin.[31]

Risdiplam

Risdiplam (Evrysdi®) was authorised for use in the EU in 2021, and is indicated for patients with SMA type I, type II, or type III or with four or fewer copies of the SMN2 gene.[30] In August 2023, the license of risdiplam was extended to remove the previous requirement that patients be at least two months of age at treatment initiation.[170] Risdiplam initiation is now licensed from birth. It is not licensed for patients with type IV disease unless they have four or fewer copies of the SMN2 gene. Risdiplam modifies *SMN2* pre-mRNA splicing leading to increased production of more functional and stable full-length SMN protein.[179] Unlike nusinersen which is administered intrathecally, risdiplam is administered orally, and has been shown to have good bioavailability in both the CNS and peripheral nervous system.[29, 30] The recommended dose is determined by age and body weight, up to a maximum dose of 5mg daily, administered once daily as an oral solution.[30] Treatment may continue for an indefinite duration.

Common adverse effects as described in the SPC include diarrhoea, nausea, mouth ulcerations and aphthous ulcers, rash, headache, pyrexia, urinary tract infection and arthralgia.[30]

5.3.2 Licensing and reimbursement in Ireland

The EMA licensing and reimbursement status for each of the three drugs are presented in Tables 5.2 (symptomatic patient context) and 5.3 (presymptomatic patient context) according to the SMA type and *SMN2* copy number, respectively.[29-31, 173-175] The three drugs differ in the scope of the SMA population covered by their respective licenses. The EMA license is broadest for nusinersen which is licensed for all patients with 5q SMA provided the risk/benefit balance is positive.[29] Risdiplam is not licensed for patients with five or more copies of *SMN2* unless they have type I to III disease.[180] OA is licensed for those with 5q SMA with a bi-allelic mutation in the *SMN1* gene and a clinical diagnosis of SMA type I or three or fewer copies of the *SMN2* gene; it is not licensed for patients with more than three copies of *SMN2* unless they have type I disease.[31]

These drugs are associated with very high drug acquisition costs. Annual costs based on the list price were estimated, using published national guidelines for the calculation of drug costs, as approximately €255,000 per patient for each of nusinersen and risdiplam (costs include VAT where appropriate - see Table 5.1).[171-173] OA is administered as a one-off treatment, with a cost to the HSE (based on the list price) of €2.2 million per patient (including VAT).[171, 172] Following critical appraisal of the economic evaluations submitted by the marketing authorisation holders for each drug, the National Centre for Pharmacoeconomics found that the treatments were not cost-effective compared with best supportive care and recommended that the drugs should not be considered for reimbursement unless cost effectiveness could be improved relative to existing treatments.[181-183] Following confidential price negotiations, the HSE approved reimbursement, but with some restrictions beyond the product license.

Managed access protocols are in place for all three drugs which restrict reimbursement. Approvals are on a named patient basis, subject to the patient meeting the pre-defined eligibility criteria. The net drug acquisition costs are anticipated to be lower than the publicly available list price (ex-factory price or reimbursement price), but this cannot be confirmed due to the confidential nature of the agreements.[167, 173-175]

The primary eligibility criteria are listed in Table 5.2 and Table 5.3 for symptomatic and presymptomatic patients, respectively. In addition to symptom status, criteria include type of SMA, number of *SMN2* copies and patient age.

Drug reimbursement for patients with symptomatic disease

For patients with symptomatic disease, no treatment is reimbursed for those with type 0 or type IV disease, or for those aged 18 years or over at treatment initiation. For those aged under 18 years at treatment initiation, nusinersen and risdiplam are reimbursed for those with type I, II or III disease.[173, 174] However, reimbursement of risdiplam is further restricted to those aged two months of age and older.[173] While OA is reimbursed for patients with type I disease, the upper age limit for reimbursement is not stated; however, it is noted that there is limited experience in those aged more than two years.[175]

For ongoing nusinersen and risdiplam reimbursement, clinicians are required to declare one or more assessment scales that are used to provide details of the patient's physical presentation at baseline and to assess treatment effectiveness.[173, 174] The choice of scale is dependent on the patient's motor ability at baseline and clinician preference. For nusinersen, patients are formally assessed at baseline, just prior to dose seven, and every four months thereafter. For risdiplam, patients are formally assessed at baseline and every six months thereafter. For both drugs, if a

patient experiences disease progression beyond that detailed within the managed access protocol, treatment should be discontinued.[173, 174]

Drug reimbursement for patients with presymptomatic disease

As a screening programme for SMA is not in place in Ireland, to date, few presymptomatic patients have been identified for treatment. The current managed access protocol for OA states that OA is reimbursed for presymptomatic patients with one, two or three *SMN2* copies; the upper age limit at which treatment may be initiated is unclear; however, there is limited experience in those aged more than two years.[175] For nusinersen and risdiplam, a clinical diagnosis of SMA is an explicit eligibility criterion.[173, 174]

For presymptomatic patients, while there are differences in the licensing indications and reimbursement criteria, the managed access protocols indicate that at least one treatment option is available for patients with between one and three *SMN2* copies. However, it is noted that current reimbursement criteria were devised based on the existing mode of presentation of patients with SMA; that is, they do not take account of a screening programme for SMA potentially being implemented.[166, 167] Accordingly, the criteria outlined may be adjusted by the HSE in the future. Reimbursement arrangements in the context of screening would need to be clarified.

Table 5.2 EMA licensing and HSE reimbursement status of drugs used to treat patients with symptomatic SMA

Drug (Age at treatment initiation)		SMA type			
		Type I	**Type II**	**Type III**	**Type IV**
Onasemnogene abeparvovec Upper age limit for reimbursement is unclear.		Reimbursed	Not reimbursed in symptomatic patients. (Licensed only if the patient has ≤3 copies of *SMN2*).		
Nusinersen	<18 years	Reimbursed			N/A as type IV is adult onset.
	≥18 years	N/A	N/A	Not reimbursed.	
Risdiplam	< 2 months	Not reimbursed.	N/A as Types II to IV have an age of onset ≥ 2months		
	≥ 2 months to < 18 years	Reimbursed			N/A as type IV is adult onset.
	≥18 years	N/A		Not reimbursed	
Summary		At least one licensed treatment is available and reimbursed by the HSE for each of these types.			Licensed treatments are available, but no treatment is currently reimbursed by the HSE.

Key: HSE – Health Service Executive; MAP – Managed Access Programme; N/A - Not applicable; SMN - SMN – survival motor neuron.
Source: European Medicines Agency;[29-31] HSE Medicines Management Programme;[166, 173-175] HSE Corporate Pharmaceutical Unit[184, 185]

Table 5.3 EMA licensing and HSE reimbursement status of drugs for patients with presymptomatic SMA by *SMN2* copy number*

	Number of *SMN2* copies				
Drug	**1**	**2**	**3**	**4**	**5+**
Onasemnogene abeparvovec Upper age limit for reimbursement is unclear.	Reimbursed			N/A as not licensed	
Nusinersen	Licensed for use in circumstances where the clinician believes the benefit-risk balance is positive. The managed access protocol states that a clinical diagnosis of SMA is an explicit eligibility criterion for treatment.				
Risdiplam	Licensed for patients with one to four *SMN2* copies. The managed access protocol states that a clinical diagnosis of SMA is an explicit eligibility criterion for treatment.				N/A as not licensed.
Summary	At least one licensed treatment is available and is reimbursed for patients with 1 to 3 copies of *SMN2.*			While licensed treatments are available, as of September 2023, it is not reported whether these treatments are reimbursed in the presymptomatic setting.	While one treatment is licensed for use in limited circumstances, as of September 2023, it is not reported whether this treatment is reimbursed in the presymptomatic setting.

Key: MAP - Managed Access Protocol. N/A - not applicable.

* As a screening programme for SMA is not in place in Ireland, to date, few presymptomatic patients have been identified for treatment. Reimbursement criteria were devised based on the existing mode of presentation of patients with SMA; that is, they do not take account of a screening programme for SMA potentially being implemented.[166, 167]

Source: HSE Medicines Management Programme 2021, 2022, 2023,[166, 173-175] HSE Corporate Pharmaceutical Unit.[184-186]

5.4 Treatment effectiveness

The following sections aim to describe the clinical trials relating to presymptomatic treatment initiation and the trials of symptomatic initiation that were pivotal to EMA authorisation for all three SMN-dependent drugs. It also describes the results of a systematic review of published study data for all the drugs and their combinations in all SMA types which had a follow-up time greater than one year.

As described in chapter 2, a wide variety of outcome measures are used to evaluate and monitor patients. Appendix Chapter 2, Table A2.1 outlines some of the common measures used in clinical practice.[1, 28] Minimal clinically important differences (MCID), in terms of differences in points on outcome measurement scales, have been defined in the literature for the following clinical function outcome measures: Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND) (4 points), Hammersmith Infant Neurological Examination (HINE-2) (2 points), Hammersmith Functional Motor Scale – Expanded (HFSME) (3 points), Revised Upper Limb Module (RULM) (2 points) and six-minute walk test (6MWT) (30 metres).[169]

5.4.1 Treatment effectiveness and safety for presymptomatic initiation

This section aims to summarise effectiveness for presymptomatic initiation as reported in trials, identified by a search of clinicaltrials.gov. One trial each were identified for nusinersen (NURTURE),[187] OA (SPR1NT),[188, 189] and risdiplam (RAINBOWFISH).[190] The characteristics of the trials are described in Table 5.4 followed by a brief summary of key findings. Baseline characteristics, efficacy outcomes, and safety outcomes are outlined in Appendix Chapter 5, A5.1. No trials were identified that directly compared presymptomatic initiation of treatment to treatment initiation once a patient with SMA has become symptomatic.

Table 5.4 Characteristics of trials of presymptomatic treatment initiation

Trial	Drug	Trial design Completion date	Key inclusion criteria	Outcomes
NURTURE NCT02386553	Nusinersen	Phase II, open-label, single group assignment, no control arm* 27 January 2025 (estimated)	▪ Homozygous deletion or pathogenic variant of *SMN1* ▪ Two or three copies of *SMN2* ▪ 6 weeks or younger at first dose, *pre symptomatic phase* ▪ CMAP > 1mV	Primary: ▪ Time to death or respiratory intervention defined as invasive or non-invasive ventilation for ≥ 6 hours/day continuously for ≥7 days or tracheostomy. Key secondary: ▪ % developing clinically manifested SMA ▪ Motor milestone achievements: HINE, WHO, CHOP-INTEND, HFMSE ▪ Safety.
SPR1NT NCT03505099	OA	Phase III, open-label, single group assignment, no control arm 15 June 2021	▪ Age ≤6 weeks at time of dose ▪ CMAP ≥2mV at baseline ▪ Gestational age of 35 to 42 weeks ▪ Cohort 1: Patients with presymptomatic SMA type I as determined by the following features: 2 copies of *SMN2.* ▪ Cohort 2: Patients with presymptomatic SMA type II as determined by the following features: 3 copies of *SMN2.*	**Cohort 1** Primary: ▪ Number of participants who achieved sitting alone for at least 30 seconds. Secondary: ▪ Event-free survival at 14 months ▪ Number of participants who achieved the ability to maintain weight at or above the third percentile without the need for non-oral or mechanical feeding support. **Cohort 2** Primary: ▪ Number of participants who achieved standing alone for at least 3 seconds. Key Secondary: ▪ Number of participants achieved the ability to walk alone

Trial	Drug	Trial design Completion date	Key inclusion criteria	Outcomes
RAINBOWFISH NCT03779334	Risdiplam	Phase II, open-label, single group assignment, no control arm 21 January 2029 (estimated)	▪ Males and females from birth to 6 weeks of age at the time of first dose (Day 1) ▪ Gestational age of 37-42 weeks for singleton births ▪ Genetic diagnosis of 5q-autosomal recessive SMA ▪ Absence of clinical signs or symptoms at screening or at baseline that are, in the opinion of the investigator, strongly suggestive of SMA.	Primary: ▪ Percentage of participants with two copies of *SMN2* gene (excluding the known *SMN2* gene modifier mutation c.859G > C) and baseline CMAP >= 1.5 mV who are sitting without support. Key Secondary: ▪ % developing clinically manifested SMA ▪ Time to death and or permanent ventilation ▪ % alive without permanent ventilation ▪ % alive ▪ % who attain motor milestones assessed by HINE ▪ % sitting without support for 5 seconds ▪ % sitting without support for 30 seconds ▪ Change from baseline in: CHOP-INTEND motor function scale, HFMSE ▪ Incidence of AEs and or SAEs.

Key: AE – adverse event; CHOP-INTEND - Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; CMAP - compound muscle action potential; HINE - Hammersmith Infant Neurological Examination; HFMSE - Hammersmith Functional Motor Scale – Expanded; OA - Onasemnogene abeparvovec; SAE – serious adverse event; SMA – spinal muscular atrophy; *SMN* - survival motor neuron; WHO - World Health Organization.
* When possible, comparisons were made between trial participants and siblings with SMA who were not treated with nusinersen.

Three trials (two of which are ongoing) were identified which aimed to evaluate presymptomatic initiation of either nusinersen, OA, or risdiplam in infants with genetically confirmed SMA. All three trials were single armed, without a comparison group, limiting the ability to make strong conclusions regarding the effectiveness of the treatment or to compare between the drugs. Interim published data from these trials reflected follow-up data ranging from 12 months (risdiplam) to a median of 2.9 years (nusinersen) for between six (risdiplam) and 29 (OA) patients. The reported data were limited to individuals with two or three copies of *SMN2*. Across the three trials, all patients were alive at follow up, with no patient requiring permanent mechanical ventilation. Functional outcome data indicated that the majority of children achieved their motor milestones within the WHO normal development range. Few safety concerns were identified in the nusinersen and OA clinical trials examined but safety data has not been published in a peer-reviewed journal for the risdiplam trial. When compared with data from a natural history cohort, data for OA suggest presymptomatic treatment initiation in individuals with two to three copies of *SMN2* is associated with marked developmental improvements and event-free survival. Additionally, when compared to siblings with SMA who were not treated with nusinersen, the data suggest that presymptomatic treatment with nusinersen is associated with improvements in motor milestone achievement.

5.4.2 Treatment effectiveness and safety for symptomatic initiation

This section describes the effectiveness of treatments in children who were symptomatic at treatment initiation. The trials were identified from the EMA European public assessment reports (EPARs) for each of the drugs.[29-31] Two trials were identified for nusinersen (ENDEAR and CHERISH),[191, 192] one trial for OA (STR1VE (also known as STR1VE-US to differentiate from STR1VE-EU which occurred later in the EU)),[193] and two trials were identified for risdiplam (FIREFIRE and SUNFISH).[194-196] The trial characteristics are described in Table 5.5, followed by a brief summary of their key findings. A summary of a systematic review which included articles that aimed to assess mid- and long-term (at least 12 months) data for patients with all types of SMA treated with any of the licensed drugs, including combinations thereof is also provided. More detailed information on the trials for symptomatic initiation and the systematic review is provided in Appendix Chapter 5, A5.2 and A5.3 respectively.

Table 5.5 Characteristics of trials of symptomatic treatment initiation

Trial	Drug	Trial design Completion date	Key inclusion criteria	Outcomes
ENDEAR NCT02193074	Nusinersen	Phase III, randomised, quadruple blinded, sham-control 21 November 2016	▪ Born (gestational age) between 37 and 42 weeks ▪ Medically diagnosed with SMA ▪ Have *SMN2* copy number = 2 ▪ Shown signs and symptoms of SMA when aged less than 6 months old.	Primary: ▪ % motor milestone responders as assessed by HINE ▪ Time to death or permanent ventilation. Key Secondary: ▪ % CHOP-INTEND responders ▪ Proportion who have died by given time thresholds ▪ % not requiring permanent ventilation ▪ % CMAP responders ▪ Time to death or permanent ventilation in the subgroup above/below the study median disease durations ▪ Number of AEs, SAEs, and discontinuation due to AEs.
CHERISH NCT02292537	Nusinersen	Phase III, randomised, quadruple blinded, sham-control 20 February 2017	▪ Medically diagnosed with SMA ▪ Onset of symptoms greater than six months of age ▪ HFMSE score >= 10 and <= to 54 at screening ▪ Aged between 2 and 12 years	Primary: ▪ Change from baseline in HFMSE score at month 15. Key Secondary: ▪ Proportion with 3 point increase from baseline HFSME score at month 15 ▪ Proportion who achieved new motor milestones at month 15 ▪ Number of new milestones achieved per participant ▪ Change from baseline in RULM test ▪ Number of AEs and or SAEs.
STR1VE NCT03306277	OA	Phase III, open-label, no control arm	▪ SMA type I with homozygous deletion or pathogenic variant of *SMN1*	Primary: ▪ Achievement of independent sitting for at least 30 seconds.

Trial	Drug	Trial design Completion date	Key inclusion criteria	Outcomes
		12 November 2019	▪ One or two copies of *SMN2* ▪ Less than six months of age at time of injection	▪ Event-free survival defined as absence of death or permanent ventilation (that is, tracheostomy or ≥16 hours daily non -invasive ventilation support for ≥14 days in the absence of acute reversible illness or perioperative ventilation). Secondary: ▪ Ability to thrive ▪ Ventilatory support independence.
FIREFISH NCT02913482	Risdiplam	Phase II/III, open-label, sequential assignment (no control arm) 17 November 2023 (estimated)	▪ Clinical history, signs or symptoms attributable to type I SMA with onset after 28 days but prior to the age of 3 months ▪ Gestational age of 37 to 42 weeks ▪ Confirmed diagnosis of 5q-autosomal recessive SMA ▪ Participants has 2 *SMN2* gene copies, as confirmed by central testing	**Part 1** Primary: ▪ Select Part 2 dose of risdiplam. Key Secondary: ▪ Number of AEs and or SAEs. Post hoc exploratory efficacy outcomes: ▪ Event-free survival (defined as alive without the use of permanent ventilation, in the absence of, or after the resolution of, an acute reversible event) ▪ Select motor milestone achievements including assessments by BSID-III, CHOP-INTEND, HINE-II.

Trial	Drug	Trial design Completion date	Key inclusion criteria	Outcomes
			▪ Body weight >= 3rd percentile for age	**Part 2** Primary: ▪ % of infants who are sitting without support for at least 5 seconds as assessed by BSID-III. Key Secondary: ▪ Select motor milestone achievements including assessments by BSID-III, CHOP-INTEND, HINE-II. ▪ Time to death ▪ Time to death or permanent ventilation ▪ Time to permanent ventilation ▪ Number of AEs and or SAEs.
SUNFISH NCT02908685	Risdiplam	Phase II/III, double blind. Sequential assignment, risdiplam vs. sham 2 September 2023 (estimated)	▪ Confirmed diagnosis of SMA ▪ Ages 2 to 25 ▪ Part 1: type II or III SMA ambulant or non-ambulant ▪ Part 2: type II or III SMA non-ambulant; RULM entry item A greater than or equal to 2; and ability to sit independently as assessed by item 9 of the MFM	**Part 1** Primary: ▪ Dose finding ▪ Change in MFM-32. Key Secondary: ▪ Safety. **Part 2** Primary ▪ Change in MFM-32. Secondary ▪ Motor milestones: specific MFM-32 items, RULM ▪ Safety.

Key: AE – adverse event; BSID-III; Bayley Scales of Infant and Toddler Development Third Edition; CHOP-INTEND - Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; HFMSE - Hammersmith Functional Motor Scale–Expanded; HINE - Hammersmith Infant Neurological Examination; MFM-32 - Motor Function Measure 32; OA - Onasemnogene abeparvovec; RULM - Revised Upper Limb Module; SAE – serious adverse event; SMA – spinal muscular atrophy; SMN - survival motor neuron; WHO - World Health Organization.

Five pivotal trials (two of which are ongoing) were identified which informed the EMA authorisation of nusinersen, OA and risdiplam in patients with genetically confirmed SMA. Published data from these trials reflect follow-up data ranging from six months (nusinersen) to 18 months (OA), for between 22 (OA) and 180 (risdiplam) patients. In both randomised controlled trials (RCTs) of nusinersen, statistically significant improvements in motor milestones were demonstrated for the nusinersen group compared to control. The trial for OA was single arm; however, results were compared with historical data, suggesting that treatment initiation in individuals with two copies of *SMN2*, and age less than six months at time of treatment is associated with developmental improvements compared to the natural history of untreated cases of SMA. The trial data for risdiplam were limited to 12-month follow-up data from a single arm exploratory study (n=17 participants with symptomatic SMA with two copies of *SMN2* and aged between one and seven months of age at time of enrolment) and interim results from an RCT (n=180 participants with SMA type II or III and aged between 2 and 25 years of age) with the latter demonstrating improvement in functional score outcomes compared to control. Given the short follow-up for these trials it is not known if the observed improvements in functional outcomes will be maintained. While a high proportion of participants experienced adverse events, only a small proportion were considered possibly or definitely treatment-related in the clinical trials examined for nusinersen and risdiplam. In the clinical trial of OA, 14% of participants (n =3) experienced a serious treatment-related adverse event.

From the clinical trials examined, there was limited evidence that earlier treatment leads to better outcomes than later treatment. In ENDEAR, which examined nusinersen in patients with type I SMA and two *SMN2* copies, the treatment effect was numerically greater in those with a shorter disease duration compared to those with a longer disease duration. However, a statistical analysis to formally test if there was a significant difference in treatment effects between subgroups was not conducted. (In the subgroup of participants with disease duration of less than 13.1 weeks at study initiation (median disease duration in the study), 30 (77%) participants in the nusinersen group were alive and without the use of permanent ventilation compared to seven (33%) participants in the sham group (HR: 0.24, 95% CI: 0.10 to 0.58). In the subgroup of participants with disease duration > 13.1 weeks at study initiation, 19 (46%) participants in the nusinersen group were alive and without the use of permanent ventilation compared to six (30%) participants in the sham group (HR = 0.84, 95% CI: 0.43 to 1.67).) CHERISH examined nusinersen in cases where onset of symptoms occurred later than six months of age. An analyses of the change in the Hammersmith Functional Motor Scale–Expanded (HFMSE) score, from baseline to month 15, according to age and disease duration, was presented graphically in the trial publication. Using this evidence they reported greater improvements in both younger children and in those who received treatment

earlier in their disease course. The magnitude of the difference was not quantified numerically and statistical tests of significance for the subgroup analysis were not reported.

Additionally, a relevant systematic review published in 2022 was identified during scoping.[169] This review which included articles published up to June 2021 aimed to assess mid- and long-term (at least 12 months) data for patients with all types of SMA treated with any of the licensed drugs, including combinations thereof. Both clinical trials and observational studies were eligible for inclusion. The review was rated as 'Low' overall confidence on AMSTAR-2 due to one critical flaw (authors did not include a list of excluded studies and justify the exclusions) and multiple non-critical weaknesses.

A total of 22 studies met the inclusion criteria for this systematic review; 19 studies assessed nusinersen, one study assessed OA, and two studies assessed combination therapy of nusinersen and OA. No studies which assessed risdiplam met the inclusion criteria. Data were limited to studies relating to patients who were symptomatic at treatment onset. Six studies enrolled only adults, three only enrolled children and 13 enrolled both. Follow-up ranged from 12 months to 5.2 years. The review authors identified a potential conflict of interest by the authors in 21 publications, with seven studies noted to be manufacturer-funded. Most of the studies were graded as being at moderate risk of bias. Results by drug and SMA type are described below. The review authors highlighted the large quantity of missing data in the included studies, as well as substantial heterogeneity between the studies, limiting comparability.

The review authors noted that nusinersen and OA improved motor endpoints in patients with SMA type I, while nusinersen was associated with small improvements or stabilisation of motor endpoints with the other SMA types, with some deterioration observed. The review authors noted that this finding of clinical benefit was consistent with the findings of the pivotal trials that informed the licensing of these drugs. However, the large quantity of missing data reported in the included studies and the substantial heterogeneity between studies were noted as limitations. This combined with the short-term data, emphasised the need for ongoing monitoring to confirm the long-term safety and effectiveness of these drugs. Detailed results from the systematic review are presented in Appendix Chapter 5, A5.3.

5.4.3 Treatment effectiveness: presymptomatic versus symptomatic treatment initiation

5.4.3.1 Nusinersen

No trials comparing presymptomatic with symptomatic nusinersen initiation were identified. Therefore, to compare outcomes, it is necessary to compare the outcomes

observed in the NURTURE trial in presymptomatic patients to those of ENDEAR, which included patients with symptomatic disease. However, it is very difficult to conduct a fair comparison given important differences in the prognostic baseline characteristics across both studies. For example, NURTURE included patients with two or three copies of *SMN2* who were presymptomatic. The authors reported that approximately half of these patients would be expected to develop type I disease; the remainder would be expected to develop type II or III disease. However these proportions based on historic distributions may have overestimated the proportion with likely type I disease included in the trial given that those with early onset symptoms would have been ineligible for inclusion. In contrast, ENDEAR only included patients with two copies of *SMN2* who were all diagnosed with type I SMA. Given these differences, it would be expected that patients in ENDEAR would have worse outcomes compared to those enrolled in NURTURE. This was observed in the trials. By the end of the ENDEAR study, 31/80 (39%) nusinersen-treated infants with type I SMA died or required permanent ventilation. In contrast, all 25 NURTURE participants were alive without permanent ventilation at the end of the study.

The difference in outcomes cannot be fully explained by the differences in the baseline characteristics as a substantial proportion of patients in the NURTURE trial would have been expected to develop type I disease and respond in a similar way to those in the ENDEAR trial. Therefore, the more favourable outcomes in the NURTURE study may be partially due to the presymptomatic initiation of nusinersen in this study.

5.4.3.2 Onasemnogene abeparvovec

No trials comparing presymptomatic versus symptomatic initiation of OA were identified. A comparison between the outcomes observed in Cohort 1 of SPR1NT (presymptomatic) and STR1VE (symptomatic) is described as both analyses included patients with two *SMN2* copy numbers who have or who are expected to develop type I SMA. While all 14 patients (100%) in SPR1NT (presymptomatic) were able to sit independently for at least 30 seconds at their 18 months of age study visit, only 13 (59%) of patients in STR1VE (symptomatic) met this milestone at this time point.

For the endpoint event free survival (defined as absence of death or permanent ventilation) at the 14 month study visit, all 14 patients were event free in SPR1NT (presymptomatic). In contrast, there were 20 (91%) participants with event-free survival in STR1VE (symptomatic). However, it is important to note that that are important differences in the baseline characteristics between both groups that may be responsible for some of the difference in outcomes. Patients with the worst prognosis were excluded from SPR1NT given they developed symptoms in the short time before they could be enrolled and receive treatment.

5.4.3.3 Risdiplam

There were insufficient data to compare outcomes for presymptomatic versus symptomatic initiation across risdiplam trials.

5.4.3.4 Summary of key results for comparison of outcomes between presymptomatic initiation versus symptomatic initiation of treatment

No trials were identified that compared presymptomatic versus symptomatic initiation. However, unadjusted naïve comparison of outcomes for patients expected to develop type I SMA treated with nusinersen or OA, suggests that presymptomatic treatment may lead to improved outcomes compared with symptomatic initiation. However, the difference in prognostic variables across studies mean that these differences are not solely due to the timing of treatment and the potential incremental benefit of presymptomatic versus symptomatic treatment is expected to be less than the difference in outcomes observed here. Further, indirect and unadjusted naive comparison such as these are heavily prone to bias. This bias, combined with very small patient numbers, means it is not possible to exclude other confounding factors and or random variation as being responsible for the difference in patient outcomes between both trials.

5.5 Discussion

The treatment landscape for SMA has changed substantially in recent years. Prior to 2017, treatment for SMA was limited to supportive therapies. As of August 2023, three survival motor neuron (SMN) dependent drugs have now been licensed by the European Medicines Agency (EMA): nusinersen (Spinraza®), onasemnogene abeparvovec (Zolgensma®) (OA) and risdiplam (Evrysdi®). There are differences between these treatments in terms of their mechanism of action and their administration schedules.

As of August 2023, international consensus guidelines have not been developed to guide the choice of one specific disease-modifying treatment versus another. In the context of any screening programme for SMA being introduced in Ireland, a working group of stakeholders, including clinical specialists, would need to be established in order to outline the associated pathways, including the treatment pathway. A treatment pathway is likely to be influenced by the most up-to-date evidence with respect to treatment effectiveness and the access arrangements for the relevant treatments at that time (that is, the reimbursement arrangements in place), in addition to factors relating to patient experience. Generally, it is important to note that treatment of SMA may change substantially in the coming years as further evidence emerges. This may include use of bridging therapy, use of combinations of treatment, or retreatment of patients. Given the highly active clinical trial landscape

in the field of SMA, the range of treatments available, their licensing in different settings, guidelines for treatment, and funding arrangements are likely to continue to evolve. As noted, current funding arrangements for SMA treatments available in Ireland were devised in the absence of a potential screening programme. Such access would need to be clarified in the context of screening.

Evidence for treatment effectiveness

SMA is associated with progressive and irreversible destruction of the nerve cells in the brain and spinal cord, therefore the principle is to prevent or minimise this destruction. The available clinical data indicate that the treatments provide a benefit; however, what is uncertain is the duration of this benefit, the relative effectiveness of the treatment options and when treatment should be initiated for individuals who are unlikely to become symptomatic for a number of years.

This chapter presented efficacy data from trials of each of presymptomatic and symptomatic initiation of treatment, followed by consideration of the relative benefit of treatment in the presymptomatic setting versus the symptomatic setting (that is, the benefit associated with earlier treatment, as would be expected to occur under screening).

The **presymptomatic** trials are important for this review, as, if newborn bloodspot screening for SMA were to be introduced, the majority of cases of SMA would likely be identified prior to symptom onset. The trials described here for both nusinersen and OA demonstrated favourable outcomes in terms of survival, and functional outcomes for trial participants, with limited safety concerns. However, it is not possible to determine the efficacy in patients with presymptomatic SMA with one copy or four or more copies of *SMN2* as the trials only included participants with two or three copies of *SMN2.* Additionally, the trials were all single arm, and therefore comparisons to a control group were not performed. The OA trial investigators did include comparisons to a historical natural cohort, which demonstrated significant differences in terms of motor milestones for the group of presymptomatic patients with SMA who received OA compared to the untreated cohort. Additionally, when compared to siblings with SMA who were not treated with nusinersen, the data for nusinersen suggest that presymptomatic treatment with nusinersen is associated with improvements in motor milestone achievement. However, there are clear challenges with the methods given the potential for baseline differences between groups. To note, only interim results for the pivotal presymptomatic trials of nusinersen (NURTURE) and risdiplam (RAINBOWFISH) are currently available. With longer follow-up, published results may differ.

Trials of **symptomatic** initiation (the pivotal trials for the EMA approval) were also described in this chapter as these represent the majority of the existing evidence base relating to SMA treatment. These trial data are relevant for a number of

reasons. Firstly, even in the context of newborn bloodspot screening which can enable earlier detection and treatment, there is evidence from existing screening programmes that some patients are symptomatic prior to treatment initiation. Secondly, these trials contribute to overall evidence of efficacy and safety. Clinical evidence for each drug is not available for every SMA type and it is noted that the EMA licenses were granted based on the extrapolation of benefit for some groups. Given the relatively recent availability of these treatments (drugs authorised between 2017 and 2021), there is limited evidence on the long term outcomes and whether benefits will be sustained over time. Most of the trials demonstrated the efficacy and safety of the treatments in a younger cohort of patients with SMA, similar to those that would likely be identified by newborn bloodspot screening. While the interim results for risdiplam (SUNFISH) also demonstrated favourable outcomes, eligibility requirements for the trial required participants to be between two and 25 years of age, making this trial potentially less relevant for this HTA, where it is expected that patients with SMA would be identified, and potentially treated, at a much younger age.

If newborn bloodspot screening for SMA were to be introduced, some patients with SMA would be treated in the presymptomatic period, or earlier in the course of symptom development compared to identification in the absence of screening. Therefore it is important to understand whether **earlier treatment** leads to better outcomes than later treatment. No trials were identified that directly compared presymptomatic initiation of treatment to treatment once a patient with SMA has become symptomatic. As outlined in chapter 2, SMA can be associated with significant morbidity and mortality due to progressive and irreversible destruction of nerve cells in the brain and cord. There would therefore be ethical challenges associated with the initiation of such studies in patients who have few copies of *SMN2*. However, some limited evidence was identified with respect to a potential treatment benefit for early versus later nusinersen treatment initiation in symptomatic patients based on subgroup analysis from the ENDEAR and the CHERISH trials. Furthermore, unadjusted naïve comparison of outcomes for patients expected to develop type I disease, treated with nusinersen or OA, suggest that presymptomatic treatment may lead to improved functional outcomes compared to symptomatic initiation. Limitations of this comparison are however noted.

In addition to the systematic review referenced within this chapter (section 5.4.2.5), a further relevant systematic review was published in June 2023;[163] this review included the same clinical trials examining presymptomatic initiation as those included within this chapter. However, it also included additional data presented at international conferences which have not been published in peer reviewed journals. Amalgamating results by copy number rather than treatment type, the authors found that, of 28 children with three copies of *SMN2*, all who received treatment

were able to walk independently. While four of these children (14%) had mild motor delays, 24 (86%) developed normally. The motor development of the 33 patients with two copies of *SMN2* was more heterogeneous. All patients were able to sit independently, but only 23 (70%) did so before nine months of age as defined by the World Health Organisation's (WHO) developmental milestones' window. Twenty-three (70%) were able to walk independently, but only 12 did so before the age of 18 months. Importantly, the children continued to progress developmentally throughout the observation periods, which, in the case of nusinersen, followed children to five years of age. As the review included the same trials as those within the present chapter, no data were identified for patients with one *SMN2* copy or more than three *SMN2* copies.

The impact of earlier treatment can be further explored indirectly by examining studies that looked at the clinical effectiveness of screening. However, it is important to note that evaluating presymptomatic versus symptomatic treatment is not directly comparable to evaluating the clinical effectiveness of screening; this is because some patients identified in a screening programme will already be symptomatic by the time treatment is initiated. Further, there are potentially some screened patients who may never have presented; such patients, when treated in the trials of presymptomatic treatment initiation, appear to benefit. However, given the uncertainty around prognosis, as well as the delivery of treatment presymptomatically, these benefits may not reflect actual clinical improvement/gain, rather what would have been the child's normal development in the absence of treatment. These studies were explored in chapter 4, where all three studies identified presented a potential positive impact of screening on morbidity. This benefit is inherently linked to the long term effectiveness data of disease-modifying treatments. Limitations in the evidence base including small sample sizes and the limited duration of studies are similar across both chapters. These limitations and the ethical challenges associated with generating additional data mean it is difficult to assess the cost effectiveness of screening for SMA. This is explored further in chapter 6 (systematic review of cost-effectiveness of screening).

Availability within the publicly funded healthcare system, and implications for screening decision-making

For completeness, clinical evidence for presymptomatic and symptomatic initiation of all three SMN-dependent treatments have been presented. However, it is important to note that some of the evidence relates to cohorts for whom the drugs are not currently reimbursed. Under existing arrangements, nusinersen and risdiplam are not reimbursed for those aged over 18 years at treatment initiation. OA is only reimbursed for presymptomatic patients who have three or fewer copies of *SMN2* and those with type I disease, that is, it is not reimbursed for those with type II to IV disease or for presymptomatic patients with higher *SMN2* copy numbers.

Furthermore, it is important to note that reimbursement criteria to date have been devised in the absence of a potential screening programme for SMA. These criteria may differ should a decision be made to implement screening.

As noted, under the terms of the existing HSE managed access protocol, OA is currently reimbursed for symptomatic patients with type I disease and for patients who have three or fewer copies of *SMN2* and who are presymptomatic at treatment initiation; in the case of the latter grouping, some of these patients would develop type II or III disease in the absence of treatment. Assuming the current criteria for access hold in the context of a screening programme, it is expected that screening for SMA would therefore shift the stage of diagnosis from symptomatic to presymptomatic and would increase the number of patients who are eligible for treatment with OA with the additional numbers predominantly relating to those who would be expected to develop Type II or Type III disease. It is not possible to estimate the change in clinical outcomes that would be associated with this shift for these patients given insufficient data publicly available from clinical studies to reliably assess the comparative effectiveness of immediate treatment with OA compared with later treatment with nusinersen or risdiplam. For those patients who would have developed type I disease in the absence of screening and as such would be offered OA anyway, screening would likely result in earlier treatment. There are some data to suggest improved outcomes for patients with type I disease who receive earlier treatment with OA. The financial implications of this potential shift are described in chapter 7 (organisational and budgetary implications). Also, as outlined in section 5.3.1.2, patients must be tested for, and have confirmed low AAV9 antibody titres prior to OA treatment. It is noted that exposure to AAV9 is thought to be low in the paediatric population, but nonetheless, there is a possibility that, for some patients, earlier identification through screening may allow for the administration of OA before exposure to AAV9 and the development of neutralising antibodies that would make them ineligible for treatment. Conversely, there is also likely to be a proportion of neonates who have AAV9 titre levels at birth secondary to maternal transfer. This population would not be able to receive OA until the titres wane.

Limitations

As this chapter was undertaken as an overview with a view to providing a high level summary of the evidence for the SMN-dependent treatment options rather than a comprehensive synthesis of all evidence in relation to these treatments, it is recognised that this approach is subject to a number of limitations. A de novo systematic review of the clinical literature was not conducted. Instead, the pivotal trials and the results of a 2022 review were summarised, albeit noting that this review was limited to studies published prior to June 2021. Additional studies have been published, some of which may now include longer follow-up data. A formal

quality appraisal of the included clinical trials was not conducted, however limitations of the included studies have been highlighted throughout. There may be further evidence for the drugs in other trials that were not included in this report (for example, initiation of the drugs in late childhood and or adulthood). Additionally, for some of the clinical studies, updated results have been made available as press releases or abstract presentations. Given these results have not been peer reviewed, these results are not presented here.

5.5.1 Conclusion

This chapter provided an overview of the SMN-dependent treatment options available for SMA and the clinical evidence available to support their use. The available evidence indicate that these drugs lead to improved outcomes in symptomatic individuals relative to the natural history of the disease. Less evidence is available for presymptomatic individuals, but there is evidence of improvements for those with two or three copies of *SMN2*. Clinical evidence for each drug is not available for every SMA type and *SMN2* copy number combination and the EMA licenses were granted based on the extrapolation of benefit for some SMA types. While there is sufficient evidence to conclude the positive benefit-risk balance of treatment, the small trial sizes, short follow-up and lack of comparative data for many cohorts limit the ability to make strong conclusions regarding the size or duration of the treatment effects or the comparative effectiveness of treatment initiation in the presymptomatic versus symptomatic phase of the disease. The evidence base continues to evolve; alongside this, correspondingly, the availability of treatments and the associated treatment pathways are subject to change.

There are three SMN-dependent drugs licensed for patients with SMA who present in either the presymptomatic or symptomatic phase. At present, the published managed access protocol for OA allows for treatment of patients with three or fewer copies of *SMN2* who are identified presymptomatically.

Therefore, with respect to the NSAC criteria for appraising the viability, effectiveness and appropriateness of a screening programme, and acknowledging the limitations identified above, evidence identified within this chapter supports the criterion that there should be an effective intervention for patients identified through screening. This stated, it must be acknowledged that while treatments are available for SMA, reimbursement arrangements have not been agreed in the context of screening and would need to be clarified.

6 Systematic review of cost effectiveness of screening

Key points

- A systematic review was undertaken to synthesise and critically appraise the international evidence on the cost effectiveness of newborn bloodspot screening for spinal muscular atrophy (SMA) and subsequent treatment compared with clinical presentation.
- Five studies met the inclusion criteria. Four cost utility analyses (CUAs) considered the costs and health consequences of an SMA screening programme over a long-term time horizon (≥60 years). One cost-effectiveness analysis (CEA) considered the outcomes of screening over a five-year time horizon.
- Changes in the therapeutic landscape over time and variation in methodological approaches contributed to a wide range of results in terms of cost per quality-adjusted life year (QALY) gained.
    - Compared with clinical presentation, newborn bloodspot screening for SMA was considered cost saving in two studies; in these studies, a substantial proportion of patients identified by screening were modelled as being treated with onasemnogene abeparvovec.
    - In one study, newborn bloodspot screening with nusinersen treatment, relative to clinical presentation, was considered not cost effective (adjusted incremental cost-effectiveness ratio (ICER) €231,004 per QALY) at a willingness to pay (WTP) threshold of €45,000 per QALY gained.
    - Finally, in one study, the ICER varied between not cost effective and cost saving depending on the treatment strategy.
- In sensitivity and scenario analysis, the cost of disease-modifying treatment, resource use (for example, hospitalisation), utility values and the incidence of SMA were identified as influential parameters.
- In all CUAs, the underlying evidence was based on a small number of trials, with single-arm design, small sample sizes, and short-term follow-up. Given the recent emergence of disease-modifying treatments for SMA, there is considerable uncertainty regarding the durability of the treatment effect in the longer-term and there is a lack of data for those with higher *SMN2* copy

numbers to underpin model inputs. Modelled assumptions did not reflect suggested treatment pathways in Ireland.

- In general, studies were considered to be of low to moderate quality largely due to limitations in the evidence base and due to inadequate reporting. Conflicts of interest arising from relationships with pharmaceutical companies were reported in three out of the five included studies.
- As a result of the limitations identified, the results of these analyses cannot be directly applied to the Irish setting.
- De novo modelling to inform cost effectiveness of screening in the Irish setting was not undertaken, due to the aforementioned limitations in the clinical evidence.

6.1 Introduction

The National Screening Advisory Committee (NSAC) criteria for appraising the viability, effectiveness and appropriateness of a screening programme specify that the opportunity cost of a screening programme should be economically balanced in relation to expenditure on medical care as a whole, based on evidence of cost effectiveness and resource efficiency. The HTA therefore considers both cost effectiveness and budget impact, with the aim of this chapter focusing on consideration of cost effectiveness. The specific objective of this chapter was to synthesise and critically appraise the international literature on the cost effectiveness of population-based screening for spinal muscular atrophy (SMA) compared with identification via clinical presentation. In addition, this chapter was used to inform the feasibility and appropriateness of conducting a de novo cost-utility analysis (CUA) in the Irish context.

6.2 Methods

No existing systematic reviews of the cost effectiveness of screening for SMA, relative to standard care, were identified during scoping exercises. Therefore, a de novo systematic review was undertaken in order to consider this question.

This systematic review was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria.[197]

6.2.1 Protocol

The protocol for the systematic review of cost effectiveness was registered on PROSPERO (PROSPERO ID: CRD42023412181) prior to the conduct of the review, and published on the HIQA website.[198] Full details of the methods used are available in the published versions of the protocol.

6.2.2 Review question

The PICO (Population, Intervention, Comparator, Outcomes) framework used to formulate the research question is presented in Table 6.1. Inclusion and exclusion criteria are described in full in the protocol.[198]

Table 6.1 Inclusion criteria set out in the PICO framework

Population	Newborns
Intervention	Population-based newborn bloodspot screening for SMA
Comparator	No population-based newborn bloodspot screening for SMA (Identification based on standard care)
Outcomes	ICER (for example, per life-year gained or quality-adjusted life-year) or NMB
Study design	Full economic evaluations: ▪ Cost-utility analysis ▪ Cost-effectiveness analysis ▪ Cost-benefit analysis.

Key: ICER – incremental cost-effectiveness ratio; NMB – net monetary benefit; SMA – spinal muscular atrophy.

6.2.3 Search strategy

The systematic search for this review was nested within a wider systematic search to identify studies relevant to the test accuracy and clinical effectiveness of newborn bloodspot screening for SMA. Screening was conducted for the three systematic reviews in parallel.

Electronic searches were conducted on 31 January 2023 in Medline (EBSCO), Embase (OVID) and the Cochrane Library. The electronic database search was supplemented by a search of the grey literature including Google Scholar, and websites of HTA agencies and government bodies. Backward and forward citation searching of included studies was also undertaken. Details of the electronic and grey literature search are presented in the protocol.[198]

6.2.4 Study selection

Two reviewers independently screened titles and available abstracts in Covidence®. 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. Any disagreements were resolved through discussion, or if necessary, a third reviewer.

6.2.5 Data extraction and management

Data extraction was conducted independently by two reviewers using a standardised, pre-piloted electronic data extraction form. Disagreements were resolved through discussion. The primary outcomes of interest were summary measures capturing both costs and consequences, for example, the cost per quality-adjusted life year (QALY) gained.

6.2.6 Data synthesis

There is no best practice method for synthesis of economic evidence as the approach depends on the purpose of the review.[199] Given the heterogeneity across studies in terms of methodology, and in population and healthcare system characteristics, a narrative synthesis was undertaken.

To facilitate comparison of results across countries and years, where appropriate, costs were converted to Irish Euro in accordance with national HTA guidelines.[200] Briefly, costs were transformed to a common year and currency (2021 Irish Euro) using consumer price indices (CPI) for health and purchasing power parities (PPP) (that is, adjusted incremental cost-effectiveness ratios (ICERs)). Unadjusted ICERs, as reported by included studies, and corresponding context-specific willingness-to-pay (WTP) thresholds are also presented. WTP thresholds of €20,000 and €45,000 per QALY gained were adopted as reference points for guiding interpretation of cost effectiveness as these are commonly employed in Ireland and are consistent with empirically based thresholds used in other high-income countries.[201, 202]

Where studies presented ICERs in terms of both the cost per QALY and the cost per life year gained (LYG), preference was given to the cost per QALY due to its ability to summarise the impact of the intervention on both quality and quantity of life and the availability of accepted WTP thresholds to facilitate interpretation.

6.2.7 Quality appraisal and transferability assessment

Assessment of the methodological quality of included studies was conducted using the Consensus on Health Economics Criteria (CHEC)-list.[203] The International Society for Pharmacoeconomics and Outcomes Research (ISPOR) questionnaire was used to assess the applicability of individual study findings to the Irish setting.[204] Each assessment was performed by two reviewers independently with disagreements resolved through discussion and the involvement of a third reviewer, where necessary. Critical appraisal plots (CHEC-list and ISPOR questionnaire) and cost-effectiveness planes were produced in Excel 2013.

6.3 Results

6.3.1 Search results

The systematic search for this review was nested within a wider systematic search which additionally sought studies relevant to the clinical effectiveness (chapter 5) of newborn bloodspot screening for SMA. After screening of title and abstracts, five economic evaluations met the inclusion criteria for this systematic review of cost effectiveness. Details of the study selection process are presented in the PRISMA flow diagram in Appendix Chapter 4, Figure 4.1.

6.3.2 Characteristics of included studies

Two of the five studies identified were conducted in Europe,[205, 206] and one in each of Canada,[14] Australia[207] and the US.[208] All included studies were model-based economic evaluations. Three studies presented results of both CUA and cost-effectiveness analysis (CEA)[205, 206, 208] and one study presented outcomes in terms of cost per QALY gained only.[207] One CEA expressed costs in relation to a number of outcome measures, namely the cost per case detected, cost per additional case detected, and finally cost per month of diagnostic delay avoided.[14]

Two of the five studies were funded by the manufacturers of disease modifying treatments for SMA.[205, 206]

Patient population and clinical pathway

In four studies, the model assumed that quantitative polymerase chain reaction (qPCR) from dried bloodspot samples was used to detect homozygous survival motor neuron 1 (*SMN1)* deletion in the screened cohort. Models assumed that patients with homozygous *SMN1* deletion underwent subsequent confirmatory testing using digital droplet polymerase chain reaction (ddPCR) or multiplex ligation-dependent probe amplification (MLPA), including quantification of survival motor neuron 2 *(SMN2)* copy number.[14, 205-207, 209] SMA cases caused by *SMN1* compound heterozygous variants were assumed to be undetectable due to limitations of the testing methodology.[14, 205-207, 209] Testing methodology was not clearly reported in one study.[208] In three studies, the authors stated that the addition of SMA to the newborn bloodspot screening panel would likely be associated with negligible additional resource consumption. This was because it was assumed that SMA would be identified using the same equipment used to detect other conditions already included in the newborn bloodspot screening programme, namely severe combined immunodeficiency (SCID) and X-linked agammaglobulinemia (XLA).[14, 208, 209] Further details of the components and cost of the screening pathway are outlined in Appendix Chapter 6 Table A6.1.

Of the four CUAs, one study considered a newborn bloodspot screening programme for infantile-onset SMA only (that is, type I SMA only).[208] The other three studies considered all patients with a homozygous deletion of *SMN1* (that is, all types of SMA resulting from a homozygous deletion) (Table 6.2). It was unclear if studies considered the potential for increases in SMA incidence after the introduction of screening.

In studies considering all patients with a homozygous deletion of *SMN1*, the models assumed that only patients with types I, II or III SMA would present symptomatically in the comparator cohort; costs and outcomes for cases presenting symptomatically with type IV SMA were not reported. For the screened cohort, SMA diagnosis and subsequent treatment was based on *SMN2* copy number. Assumptions regarding the SMA genotype in the screened cohort varied between studies. In one CUA based in the Australian context, pre-symptomatic cases with four or more copies of *SMN2* were not reported as positive screening tests. This model was informed by results of a one-year pilot study in New South Wales and Australian Capital Territory which had used this approach, the rationale for which was the clinical uncertainty regarding the disease course in these individuals alongside a lack of availability of an appropriate treatment option for such individuals in Australia at that time .[207] In two studies, it was assumed that patients with SMA and between two and four copies of *SMN2* would be classified as a positive screening test result and would require subsequent treatment informed by *SMN2* copy number (

Table 6.3);[205, 206] however, it was unclear how patients with homozygous deletion of *SMN1* and one copy or with more than four copies of *SMN2* were managed.

Treatment landscape

Four out of five included studies considered the costs and health consequences of SMA treatment.[205-208] The assumed therapeutic landscape for SMA varied considerably between these studies, reflecting changes over time in drug development and reimbursement (Table 6.3). Earlier studies contained only one treatment option or considered multiple base case analyses in which the cohort diagnosed with SMA were treated exclusively with either nusinersen or onasemnogene abeparvovec (OA) (rather than a treatment mix informed by clinical diagnosis and/or reimbursement criteria).[14, 208] In two studies, following a positive screening test result, subsequent treatment was based on the range of available treatment options at the time of analysis, with the relative proportion of patients receiving each treatment informed by expert opinion.[205, 206]

Assumptions relating to the SMA genotype in the screened SMA cohort or the SMA phenotype among patients presenting symptomatically, and the associated treatment options, have important implications for estimates of the long-term costs associated with a newborn bloodspot screening programme for SMA. Different treatment strategies were associated with considerably different requirements in terms of healthcare utilisation and costs. Characteristics of the treatment strategy are presented in Table 6.3.

Treatment efficacy

All four CUAs assumed that earlier treatment was associated with improved clinical outcomes, with this assumption based on short-term efficacy data from clinical trials on milestone achievement. As noted in chapter 4, there is limited comparative data directly comparing outcomes of screening and subsequent treatment with clinical presentation only. All studies used data from single arm clinical trials of available pharmacological treatments in presymptomatic and symptomatic patients as a proxy for outcomes of screening and clinical presentation, respectively.

In one study, published in 2020, a conservative approach was taken such that, in the base case analysis, additional QALYs were accumulated in the screened cohort due to a reduction in time-to-treatment only. In a secondary analysis, the authors assumed that earlier treatment is associated with improved health outcomes based on efficacy data for nusinersen from the ENDEAR trial.[191] As discussed in chapters 4 and 5, while data are limited, there is evidence to suggest improved clinical outcomes with earlier treatment. Therefore, for the purposes of this review, the secondary analysis was considered most appropriate.

In two studies, efficacy data for nusinersen from the NURTURE trial[187] was used as a proxy for early presymptomatic identification following screening, under the

inherent assumption that all screened cases would be presymptomatic at treatment initiation.[205, 207] Of note, the same efficacy was applied for treatment with either nusinersen or OA, due to the absence of OA efficacy data at the time of analysis.[205, 207] Data from trials in symptomatic patients were used to model outcomes associated with later treatment initiation.

One study conducted in the UK used data from the SPR1NT (efficacy of OA),[188, 189] NURTURE (efficacy of nusinersen)[191] and RAINBOWFISH (efficacy of risdiplam)[210] trials to estimate expected treatment outcomes associated with presymptomatic treatment.[206] Of note, the authors assumed that approximately 40% of patients with two copies of *SMN2* would be symptomatic at the time of treatment initiation in the screening cohort, based on expert opinion. For these patients, the clinical trajectory of a patient with SMA type III was assumed. Clinical inputs for the no screening cohort were based on clinical trials in symptomatically detected patients.

Table 6.2 Characteristics of study populations

Author Country	Population	Incidence (per live births) / Prevalence*	SMA phenotype (%) (symptomatic presentation)					*SMN2* copy numbers (%)† (detected by newborn bloodspot screening)			
			0	I	II	III	IV	1	2	3	4
INESSS 2021[14] Canada (Quebec)	Neonatal population participating in the Quebec Newborn Blood Screening Program	Incidence: 1 in 12,281	1.2	58.9	20.0	18.7	1.0	5.3	47.3	36.8	10.1
Jalali 2020[208] United States	Infantile onset, type I SMA	Prevalence (sic): 0.94 per 10,000 (range 0.36 to 0.83)	NA	60	NA	NA	NA	NR	NR	NR	NR
Shih 2021[207, 209] Australia (NSW/Australian Capital Territory)	Newborns	Incidence: 1 in 10,989	NR	58	29	13	NR	0	69	31	0‡
Velikanova 2022[205] The Netherlands	N = 169,680 newborns in The Netherlands (2019)	Incidence: 1 in 10,000	NR	58	29	13	NR	NR	45	33	22
Weidlich 2023[206] England	N = 585,195 newborns in England and Wales (2021)	Incidence: 1 in 10,000	NR	58	29	13	NR	NR	46.7**	25	28.3

Key: NA – not applicable; NR – not reported; NSW – New South Wales; SMA - spinal muscular atrophy; SMN - survival motor neuron.
* All reports used a single incidence value which would suggest an assumption that incidence / prevalence does not change following implementation of screening.
† Based on the information provided, no study modelled patients with more than four copies of *SMN2*.
‡ No genotypes with *SMN1* homozygous deletion and > 3 copies of *SMN2* were identified by the newborn bloodspot screening laboratory.
** Based on expert opinion, it was assumed that 40% of patients with two copies of *SMN2* would be symptomatic by the time they received treatment (before age 6 months).

Table 6.3 Characteristics of the treatment strategy

Author Country	Treatment type (treatment mix %)	Administration	Adjusted drug cost per dose† (excluding associated healthcare utilisation)
INESSS 2021[14]	NA	NA	NA
Jalali 2020[208]	Nusinersen (100%)	Four loading doses of nusinersen administered via lumbar puncture. Patients continued to receive nusinersen injections every 4 months for the duration of the model (lifetime).	€107,683
Shih 2021[207, 209]	OA or nusinersen‡	OA: one-off Nusinersen: Four loading doses in the first 2 months followed by a maintenance dose every 4 months. Applied constant life-long nusinersen treatment for both with and without newborn bloodspot screening.	OA: €923,839 Nusinersen: €45,478
Velikanova 2022[205]	OA (94%), nusinersen (6%)	OA: one time Nusinersen: 4 loading doses administered within approx. 63 days of the initial dose and a maintenance dose administered once every 4 months thereafter.	OA: €2,063,358 Nusinersen: €88,369
Weidlich 2023[206]	**Screening** <u>Presymptomatically detected:</u> ▪ 2 copies *SMN2*: 93% OA, 6% nusinersen, 0% risdiplam, 1% supportive care. ▪ 3 copies *SMN2*: 93% OA, 6% nusinersen, 0% risdiplam, 1% supportive care.	NR	NR

Author Country	Treatment type (treatment mix %)	Administration	Adjusted drug cost per dose† (excluding associated healthcare utilisation)
	▪ 4 copies *SMN2*: 0% OA, 6% nusinersen, 50% risdiplam, 44% supportive care. <u>Patients identified via screening but treated symptomatically:</u> ▪ 2 copies *SMN2*: 93% OA, 6% nusinersen, 1% supportive care. **No screening** <u>Symptomatically detected:</u> ▪ Type I: 56% OA, 2% nusinersen, 22% risdiplam, 20% supportive care. ▪ Type II: 0% OA, 10% nusinersen, 90% risdiplam, 0% supportive care. ▪ Type III: 0% OA, 10% nusinersen, 90% risdiplam, 0% supportive care.		

Key: NA – not applicable; NR – not reported; OA - onasemnogene abeparvovec; SMN - survival motor neuron.
† Costs have been adjusted based on national consumer price indices and purchasing power parities in accordance with national HTA guidelines.
‡ Modelled as alternative treatment strategies; within the report, the treatment strategies reported were nusinersen and 'gene therapy'. As onasemnogene abeparvovec (OA) was the only available gene therapy and the study references the OA trial, it is named here in the interest of clarity.

Model characteristics

All of the four CUAs modelled the long-term (≥60 years) costs and consequences associated with a newborn bloodspot screening programme for SMA comprising screening and subsequent treatment of diagnosed cases, relative to a strategy with no screening and diagnosis by clinical presentation only. Three out of the four studies used a decision tree to capture the outcomes of screening, with subsequent entry into a Markov model to project the long-term health outcomes and associated costs following diagnosis (Table 6.4).[205-207] Of these, the same model structure was used in two studies, although model inputs and assumptions differed.[205, 206] In one study, the structure was described as a Markov model only.[208] One CEA, published in 2021, restricted the time horizon to five years. This study did not incorporate costs or outcomes related to long-term disease management (for example, treatment and healthcare utilisation) due to limitations in the evidence base at the time of analysis, and in particular, the absence of comparative data on different treatment strategies and outcomes of symptomatic versus pre-symptomatic treatment.[14]

The health states considered in the Markov models were based on achievement of gross motor milestones, consistent with outcomes of relevant randomised controlled trials (RCTs) (chapter 5). Due to the absence of long-term efficacy data (range 13 months to five years' follow-up),[191, 211] outcome data related to motor milestones from short-term clinical trials were extrapolated over a lifetime time horizon. Where assumptions were reported, it was noted that the motor milestones achieved at the end of follow-up in the clinical trials were assumed to be sustained until death; this the authors suggested was due to the absence of evidence to suggest that *SMN2* protein expression stops or wanes over time.[205, 206]

Three out of five studies adopted the perspective of the healthcare system in the base case analysis,[14, 205, 206] with the remaining two studies reporting results from the societal perspective (Table 6.4).[207, 208] Discounting was performed in accordance with country-specific requirements for both costs and benefits.

Table 6.4 Model characteristics

Author Country	Intervention	Comparator	Type of analysis	Model type	Health states	Perspective	Time horizon	Discount rate
INESSS 2021[14]	Newborn bloodspot screening for SMA in the Quebec Neonatal Blood Screening Program	Clinical identification	CEA	Decision tree	NA	Public health and social services system	5 years	1.5%
Jalali 2020[208]	Universal screening and treatment of infantile-onset SMA with periodic injections of nusinersen	1. Nusinersen treatment without universal screening 2. Universal screening and no treatment 3. No screening and no treatment	CUA and CEA	Markov model	▪ SMA free ▪ Untreated SMA ▪ Treated SMA ▪ Motor milestone response ▪ PAV ▪ Death	Societal	Lifetime	3%
Shih 2021[207, 209]	Newborn bloodspot screening for SMA and early treatment with Nusinersen or onasemnogene abeparvovec	1. Nusinersen treatment without screening (primary comparator) 2. Historical cohort without screening and managed by supportive care (secondary comparator)	CUA	Decision tree and Markov model	▪ Non-sitter ▪ Sitting with support ▪ Standing with assistance ▪ Walking with assistance ▪ Walking unaided ▪ PAV/Nutrition support ▪ Death	Societal	5 years; 60 years	3%

Author Country	Intervention	Comparator	Type of analysis	Model type	Health states	Perspective	Time horizon	Discount rate
Velikanova 2022[205]	Newborn bloodspot screening for SMA and subsequent treatment	No screening - diagnosis and treatment after presentation with overt symptoms	CUA and CEA	Decision tree and Markov model	▪ Normal development ▪ Walking ▪ Sitting ▪ Not sitting ▪ PAV	Payer (base case)	Lifetime (100 years)	Costs: 4% Outcomes: 1.5%
Weidlich 2023[206]	Newborn bloodspot screening for 5q spinal muscular atrophy (pre-symptomatic or symptomatic presentation)	No screening (symptomatic presentation)	CUA	Decision tree and Markov model	▪ Normal development ▪ Walking ▪ Sitting ▪ Not sitting ▪ PAV ▪ Death	National Health Service (base case)	Lifetime (100 years)	3.5%

Key: CEA – cost-effectiveness analysis; CUA – cost-utility analysis; NA – not applicable; PAV – permanent assisted ventilation; SMA – spinal muscular atrophy.

6.3.3 Summary of findings

As noted in section 6.3.2, studies applied different treatment pathways, input parameters or assumptions underpinned by the available evidence at the time of analysis, evidence from the local context or expert opinion in the absence of empirical evidence. Therefore, results of included studies are not directly comparable.

Cost-effectiveness analysis

A CEA undertaken by INESSS reported diverse ICERs depending on the outcome measure used. The cost per additional case detected was €614,129, while the cost per case detected was €133,248. Expression of the outcome in terms of the potential for a reduction in the time to diagnosis compared with clinical presentation yielded the most favourable ICER at €22,296 per month of diagnostic delay avoided. It should be noted that there is no accepted WTP threshold to facilitate interpretation of the cost effectiveness of CEAs expressing outcomes in terms of single natural units (for example, cost per case detected), which presents challenges for their use in decision-making.[200]

For studies that reported the cost per QALY and the cost per LYG, the ICERs expressed as cost per LYG are presented in the Appendix Chapter 6, Table A6.2.[205, 206, 208] ICERS expressed as cost per QALY are discussed in the following section.

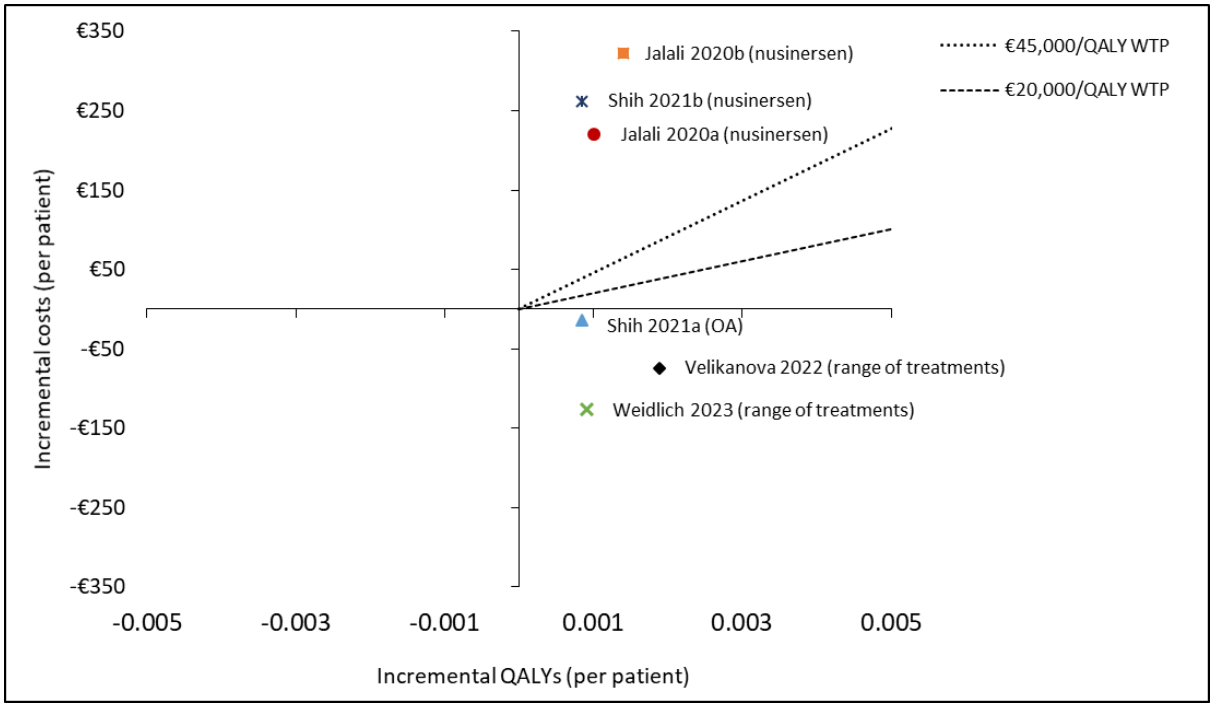
Cost-utility analyses

Results for the comparisons most applicable to the Irish context are presented below. Results for additional comparisons are presented in the Supplementary Appendix Chapter 6, Table A6.3. Four studies expressed outcomes in terms of the cost per QALY gained. Compared with no screening and clinical presentation, newborn bloodspot screening for SMA and subsequent treatment was cost saving in two studies (Figure 6.1 and Table 6.5).[205, 206] In one study, newborn bloodspot screening with nusinersen treatment was considered not cost effective relative to clinical presentation and subsequent treatment at a WTP threshold of €45,000 per QALY.[208] Finally, in one study, the ICER varied between not cost effective and cost saving depending on the treatment strategy.[207]

The treatment strategy had a considerable influence on the estimated cost-effectiveness of a newborn bloodspot screening programme relative to no screening and treatment following clinical presentation. In two studies, in which it was assumed a significant proportion of patients identified by screening would be treated with OA, newborn bloodspot screening was considered cost saving over a lifetime time horizon (Table 6.5).[205, 206] In one study, in which nusinersen was the only available treatment, newborn bloodspot screening for SMA was considered not cost

effective at a WTP threshold of €45,000 per QALY (adjusted ICER €213,206 per QALY or €231,004 per QALY, depending on the clinical inputs used) (Table 6.5).[208] In this study, the estimated cost effectiveness of the intervention was found to be highly dependent on the price per dose of nusinersen (see scenario analysis). A CUA undertaken in the Australian context presented six different treatment strategies in the base case analysis. In one analysis, compared with no newborn bloodspot screening and nusinersen treatment, newborn bloodspot screening and nusinersen treatment was found to be not cost effective over a lifetime time horizon (adjusted ICER €307,746 per QALY) (Table 6.5).[207] In a second analysis, newborn bloodspot screening and subsequent treatment with gene therapy dominated no newborn bloodspot screening and nusinersen treatment (that is, it less costly and more effective). The analysis also reported a head-to-head comparison of different newborn bloodspot screening options, with newborn bloodspot screening and gene therapy found to be cost saving compared with newborn bloodspot screening and nusinersen.[207] While the simplifying assumption of exclusive treatment with nusinersen or OA for all patients with SMA does not apply in practice due to differences in reimbursement criteria, this study illustrates that the cost effectiveness of a newborn bloodspot screening programme for SMA is highly dependent on the cost of available treatments.

Figure 6.1 ICERs presented on a cost-effectiveness plane



Key: OA - Onasemnogene abeparvovec; QALY – quality-adjusted life year; WTP – willingness-to-pay. Interventions that are more costly and more effective than the comparator lie in the north-east quadrant. In this quadrant, interventions that fall below the context-specific WTP threshold are

considered cost effective. Interventions in the south-east quadrant are less costly and more effective than the comparator (the "dominant" strategy).
For Jalali 2020a and 2020b, efficacy data were based on the ENDEAR trial and preliminary results of the NURTURE trial, respectively. Both analyses were adjusted for early and late treatment effects. Shih 2020a denotes the estimated ICER for newborn bloodspot screening and OA relative to clinical presentation and subsequent treatment with nusinersen. Shih 2020b denotes the estimated ICER for newborn bloodspot screening and nusinersen treatment relative to clinical presentation and subsequent treatment with nusinersen.

Of note, while the incremental QALY gain expressed per patient presented in Figure 6.1 is small, given the low prevalence of SMA within the screened cohort (~1 in 10,000 live births, see Table 6.2), the estimated QALY gain per child diagnosed with SMA is substantial. A CUA undertaken in the Dutch context estimated that newborn bloodspot screening and subsequent treatment was associated with 19 incremental QALYs, relative to no newborn bloodspot screening and treatment following symptomatic presentation.[205]

Interpretation of the findings with reference to WTP thresholds commonly used in Ireland largely did not change the conclusions of the underlying studies (Appendix Chapter 6, Table A6.4). In one study, interpretation of the findings with reference to a WTP threshold for ultra-rare diseases ($500,000 USD per QALY) rendered newborn bloodspot screening and subsequent treatment cost effective in 93% of simulations relative to a strategy with no newborn bloodspot screening and symptomatic presentation.[208] However, the intervention was not considered cost effective at the standard WTP threshold applied in the US context.

Table 6.5 Adjusted incremental cost-effectiveness ratio for cost-utility analyses

Author (year)	Country	Strategy	Adjusted ICER[†]	Interpretation in the Irish context[‡]
Jalali 2020[208]	US	Newborn bloodspot screening and treatment of infantile-onset SMA with nusinersen versus nusinersen treatment without universal screening (ENDEAR trial)	€213,206 per QALY	Not cost effective
		Newborn bloodspot screening and treatment of infantile-onset SMA with nusinersen, versus nusinersen treatment without universal screening (preliminary data from NURTURE trial)	€231,004 per QALY	Not cost effective
Shih 2021[207, 209]	Australia (New South Wales/Australian Capital Territory NBS pilot)	Newborn bloodspot screening for SMA and treatment with nusinersen versus no screening and nusinersen treatment	€307,746 per QALY	Not cost effective
		Newborn bloodspot screening for SMA and treatment with OA versus nusinersen treatment without screening	Dominant	Cost saving
Velikanova 2022[205]	The Netherlands	Newborn bloodspot screening for SMA and subsequent treatment versus no screening (diagnosis and treatment after symptomatic presentation)	Dominant	Cost saving
Weidlich 2023[206]	England and Wales	Newborn bloodspot screening for 5q SMA (pre-symptomatic or symptomatic identification and treatment) versus no screening (symptomatic presentation and treatment)	Dominant	Cost saving

Key: ICER – incremental cost-effectiveness ratio; QALY – quality-adjusted life year; SMA – spinal muscular atrophy; US – United States.
[†] Costs were adjusted based on national consumer price indices and purchasing power parities in accordance with national HTA guidelines.
[‡] WTP thresholds of €20,000 and €45,000 per QALY gained, commonly employed in Ireland, were used as reference points to guide interpretation of cost effectiveness.

Sensitivity analysis

Three out of four CUAs presented the results of one-way sensitivity analysis.[205-207] Of these, the results were robust to changes in all tested parameters in two studies.[205, 206] In one study conducted in the Australian context, results were sensitive to the cost of nusinersen maintenance therapy.[207] Uncertainty in the following input parameters led to the most substantial variation in estimated ICERs: the incidence of SMA,[207] utility values,[205, 206] resource use in the sitting health state,[205, 206] and disease management costs (that is, resource use for ventilated patients[206] and pharmacological treatment[207]).

Scenario analysis

All four CUAs undertook scenario analysis. Two studies conducted in Europe reported that the results were largely robust in scenario analyses.[205, 206] The influence of treatment costs on the ICER was investigated in scenario analysis in three studies.[205, 207, 208] In two studies, the cost of nusinersen was reported to have a substantial influence on the ICER.[205, 208] One study carried out in the US context undertook threshold analysis to investigate the price at which treatment with nusinersen would be considered cost effective. It was estimated that in order to be considered cost effective at the standard WTP threshold of $50,000 per QALY applied in the US context (~ €40,000 per QALY), the price per dose would need to be approximately $23,361 USD (~€18,000), that is, less than one fifth of the estimated market price at the time of analysis.[208] One study conducted in the Dutch context reported that newborn bloodspot screening and subsequent treatment was no longer dominant compared with clinical presentation when nusinersen exceeded 50% of the treatment mix.[205] If nusinersen was assumed to comprise 75% of the treatment mix, newborn bloodspot screening would no longer be considered cost effective (adjusted ICER €48,911 per QALY).[205] According to a study carried out in the Australian context, screening and treatment with OA would still be considered cost effective (adjusted ICER €12,598 per QALY) relative to clinical presentation and nusinersen treatment if the price of OA was set at the assumed upper bound ($2.1 million AUD, or approximately €1.3 million).[207]

6.3.4 Quality appraisal

Of the five studies included, four were considered moderate quality,[205-208] and one was considered low quality based on the CHEC-list criteria (Figure 6.2).[14] In general, studies provided clear descriptions of objectives, the study population and results. However, concerns were raised related to the adequacy of reporting, in particular the absence of justification for key modeling decisions.

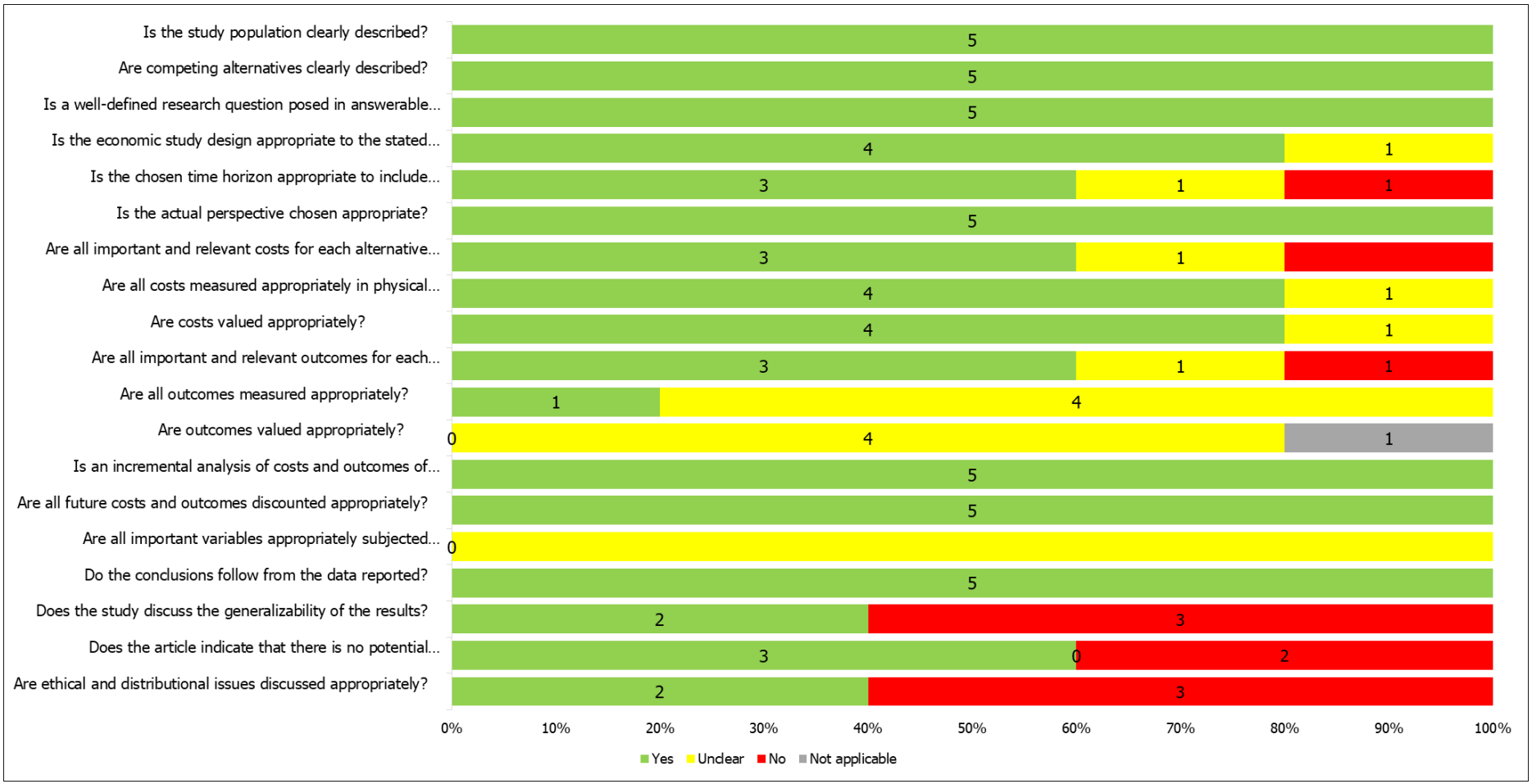
Concerns with the model structure were noted for three studies in relation to the choice of time horizon,[14] inadequate reporting of transition probabilities[205] and the Markov model structure.[208] Estimation of cost effectiveness over multiple time horizons, adopted in three models, was considered most appropriate, given considerable uncertainty about the durability of the treatment effect in the longer-term.[205-207]

Estimation of utility values for a paediatric population with a rare disease is challenging. Due to the absence of applicable preference-based values, in all analyses some or all utility values were based on proxy reports (parent/guardian or a healthcare professional) or adopted surrogate values from other diseases. Where proxy reports or surrogate values were used, whether or not assumed utility values adequately reflect health-related quality-of-life (HRQoL) in these health states is unclear.

All studies undertook sensitivity analysis, however, estimates of parameter uncertainty and distributional assumptions were not reported for all inputs.[14, 205-208] While it is acknowledged that estimates of uncertainty may be challenging to obtain for all parameters in the context of a rare disease, the choice of parameters for sensitivity analysis should be clearly reported.

In three studies, potential conflicts of interest were identified. These related to studies being sponsored by the manufacturers of disease-modifying treatments or undertaken by employees of the manufacturing companies, or one or more study authors being reported as having held membership on a scientific advisory board for a relevant drug or device manufacturer.[205-207]

Figure 6.2 Methodological quality assessment of economic evaluations using CHEC-list



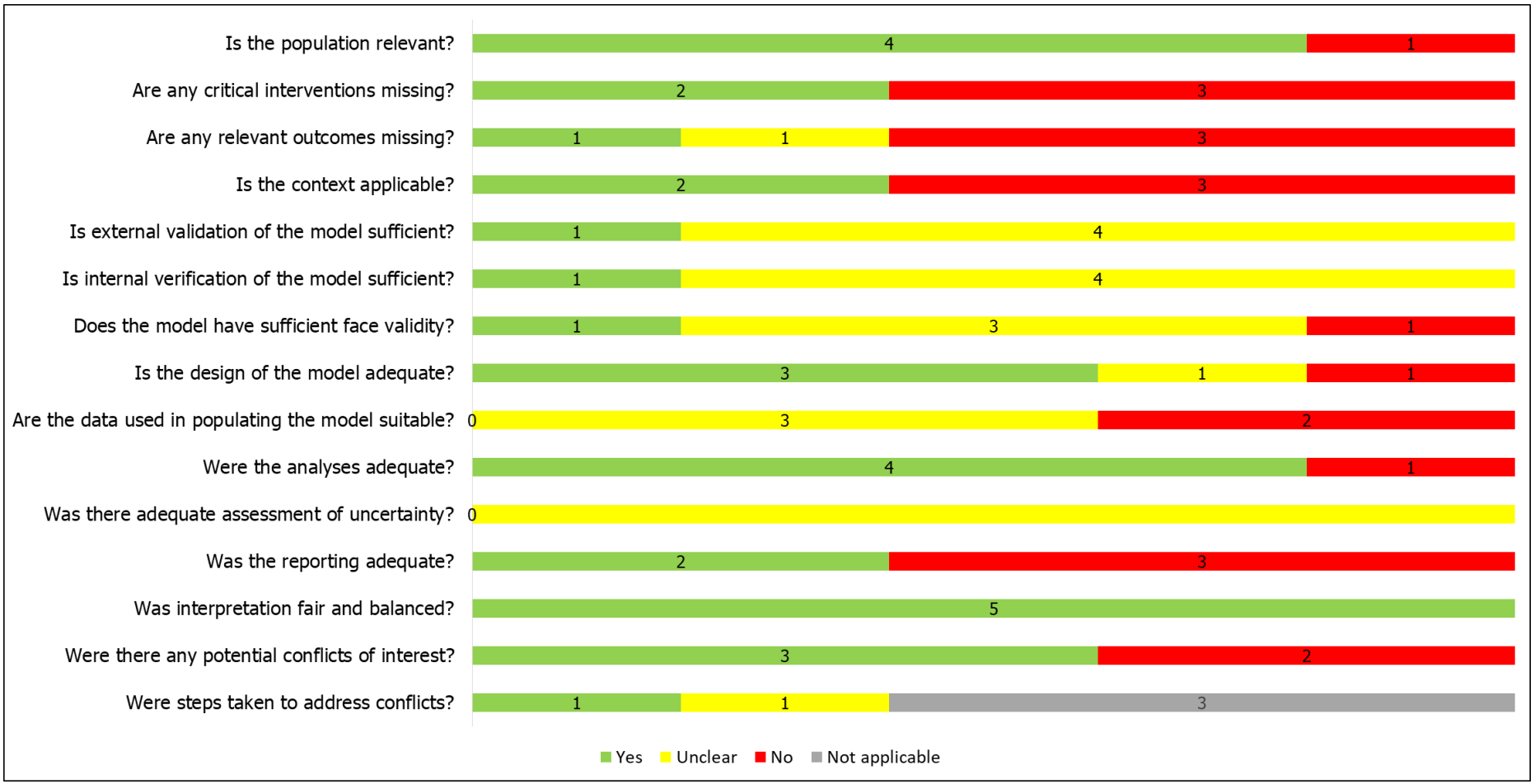
6.3.5 Transferability assessment

The results of the assessment of applicability of the included studies are illustrated in Figure 6.3. Overall, three studies were considered not applicable to the Irish context,[14, 207, 208] while two studies were considered partially applicable.[205, 206]

Three studies set in the US, Canadian and Australian contexts were not considered applicable to the Irish context due to differences in healthcare system structuring and financing,[14, 208] adoption of the societal perspective,[207, 208] restriction of the study population to SMA type I only,[208] limitation of modelled outputs to screening outcomes only,[14] and assumptions regarding the treatment mix.[207] Of note, there was large variation in modelled drug prices between studies, in particular for nusinersen (range per dose: €45,478 to €107,683). The applicability of such estimates to the Irish context is uncertain due to the potential for confidential pricing agreements which may mean the price paid by the publicly-funded healthcare system (that is, the HSE) is anticipated to be lower than the calculated cost at the published price (nusinersen: €67,899 per vial excluding VAT).[171, 172]

In the absence of agreed international clinical guidelines for patients with SMA, modelling the diagnostic and treatment pathway for all potential phenotypes and genotypes is challenging. In particular, for cases with four or more copies of *SMN2* given that countries may differ in their approach with a 'watch and wait' management strategy adopted in some contexts for these patients (Section 2.3.3). Included economic evaluations adopted diverse approaches to management of cases with homozygous *SMN1* deletion and four or more copies of *SMN2*. In one study, based on an Australian pilot study in New South Wales and Australian Capital Territory, cases identified by newborn bloodspot screening with four or more copies of *SMN2* were not included.[207] As outlined in section 4.3.3, as per the screening algorithm used in the pilot study, these were not reported as positive screens given the uncertainty regarding the clinical course and the local policy not to reimburse treatment for asymptomatic patients in this context. In two studies, it was assumed that only a proportion of patients with four or more copies of *SMN2* would access pharmacological treatment, or assumptions regarding treatment options in this cohort were not clearly stated.[205, 206] The applicability of these assumptions to the Irish context is unclear. Despite uncertainty related to the optimal diagnostic and treatment pathways for all SMA genotypes identified by screening, the two analyses conducted in Europe were considered broadly applicable in terms of the healthcare system and population characteristics.

Figure 6.3 Transferability assessment of economic evaluations to the Irish context using the ISPOR questionnaire



6.4 Discussion

This systematic review aimed to summarise the evidence on the cost effectiveness of newborn bloodspot screening for SMA relative to clinical presentation, and to assess the applicability of the evidence to the Irish context. Five studies met the inclusion criteria, including one CEA and four CUAs. In the CEA, the ICERs ranged from €639,496 per additional case detected to €23,217 per month of diagnostic delay avoided. In included CUAs, compared with clinical presentation, newborn bloodspot screening for SMA and subsequent treatment was cost saving in two studies,[205, 206] not cost effective at a WTP threshold of €45,000 per QALY in one study,[208] and finally in one study the ICER varied from not cost effective to cost saving depending on the treatment strategy.[207]

Based on the available evidence, the cost effectiveness of newborn bloodspot screening for SMA is highly dependent on the treatment strategy adopted following a positive screening test result. In general, under the modelled assumptions, treatment of patients with OA, rather than nusinersen, was associated with more favourable outcomes in terms of cost effectiveness over longer-term time horizons as a result of assumed requirements for ongoing maintenance dosing associated with nusinersen.[205-208] Importantly, in the Irish context, these treatments are not necessarily competing alternatives; while updates to reimbursement criteria may occur in the context of screening, currently there are distinct reimbursement criteria for specific SMA genotypes and/or phenotypes.[174, 175] Given that OA is currently reimbursed for presymptomatic patients with a bi-allelic deletion in *SMN1* and three or fewer copies of *SMN2*,[175] the proportion of patients eligible for treatment with OA, and therefore the cost effectiveness of an newborn bloodspot screening programme in the long-term, would likely be dependent on the outcomes of screening in the Irish context. Importantly, in all analyses where the treatment strategy included OA, it was assumed that treatment was one-off.[205-207] At present, the available evidence suggests that a durable response is maintained up to five years post-treatment.[211] Results of ongoing long-term follow-up of the START trial will be important to determine if SMN protein expression stops or wanes over time. Requirements for additional interventions would influence the cost effectiveness of a newborn bloodspot screening programme including treatment with OA.

Assumptions regarding nusinersen administration also warrant consideration. In economic evaluations, the requirement for long-term maintenance dosing is assumed. However, given the recency of nusinersen to clinical practice, it is not known if lifelong treatment with nusinersen is possible. For patients with advanced scoliosis, intrathecal drug delivery can be challenging.[212] It is plausible, however, that earlier intervention may circumvent further muscle atrophy and orthopaedic complications. The potential for progression over time resulting in scoliosis, despite

treatment, cannot be eliminated, which may present challenges for treatment administration in the longer-term, even if screening and earlier treatment were available. The estimated long-term cost effectiveness of nusinersen is highly dependent on assumptions regarding treatment suitability.

In addition, the cost effectiveness of the addition of SMA to the newborn bloodspot screening programme is dependent on the existing resources within a given healthcare system. In three studies, the authors highlighted the potential for synergies with existing conditions on the newborn bloodspot screening panel.[14, 208, 209] Similarly, in the Irish context, potential efficiencies could be achieved in terms of equipment and staff resources by concurrent addition of conditions using the same testing platforms and kits to the newborn bloodspot screening panel.

As discussed in chapter 2, in clinical practice the treatment strategy is informed by SMA phenotype for patients presenting symptomatically, or SMA genotype for patients detected by newborn bloodspot screening who are not symptomatic at the time of diagnosis. However, there are no agreed, best practice guidelines for the diagnosis and management of SMA with disease-modifying treatments. Importantly, a proportion of patients with genetically confirmed SMA that are identified through newborn bloodspot screening may remain asymptomatic or experience late-onset disease. A highly sensitive prognostic marker to identify this subpopulation is not available; while *SMN2* copy number inversely correlates with disease severity, the subpopulation with four or more copies of *SMN2* represent a particularly heterogeneous group that can experience disease onset anytime from infancy to middle age. The relationship between genotype as determined by newborn bloodspot screening and the associated treatment options was only clearly reported in one study in this systematic review.[206] In this study, it was assumed that 56% of patients with a homozygous *SMN1* deletion and four copies of *SMN2* would be managed with nusinersen or risdiplam based on expert opinion. In other studies, it was assumed that patients with four or more copies of *SMN2* would not be treated,[207] or assumptions relating to this sub-cohort were not clearly reported.[205] While a published consensus document was identified recommending treatment of patients with four copies of *SMN2*,[46] there is considerable uncertainty in the literature regarding the optimal approach to disease management for this subpopulation.

It is worth noting that in included studies, the distribution of *SMN2* copy number in the screened cohort was based on the results of international screening programmes, which at the time of analysis had largely reported data for patients with four or fewer copies of *SMN2* (either because cases with more than four copies were not identified, or not included in the definition of screen positivity). As highlighted in chapter 4 (Table 4.5), data on patients with five or more copies of

SMN2 remain limited at the time of writing. In light of the substantial uncertainty regarding the distribution of *SMN2* copy numbers in screened cohorts, and the clinical effectiveness of treatment for patients with four or more *SMN2* copies, estimating the impact of alternative definitions of screen positivity and consequent changes in clinical management pathways on the estimated of cost effectiveness of screening is extremely challenging. As longer-term follow-up data emerge, the management of patients with more than four copies of *SMN2* should be considered in future economic evaluations, both in terms of the definition of screen positivity applied, and the subsequent management pathway. However, robust clinical and epidemiological data for individual genotypes within the population with SMA are unlikely to become available in the near future.

Derivation of utility values for patients with SMA is challenging due to the nature of the disease. A 2021 systematic review of utility values for patients with SMA noted that the evidence base was largely characterised by proxy-derived estimates of unclear clinical relevance.[213] The authors reported that available estimates were frequently insufficient with respect to the requirements of HTA bodies. A systematic review of inter-rater agreement between self- and proxy-reported HRQoL in children reported that agreement was poor overall, in particular for psychosocial-related domains, which raises concerns about the applicability of proxy-derived estimates used in included CUAs.[214] Importantly, in the present systematic review certain health state utility values were identified as influential parameters in two out of three models that undertook one-way sensitivity analysis.[205, 206] The utility values applied should be representative of the HRQoL in a given health state over time. Limitations in functional capacity may impact HRQoL to different degrees over the lifespan of a patient. In addition, although the model structure in included CUAs captured important gross motor milestones consistent with motor development milestones outlined by the WHO, it is important to note that other clinically meaningful outcomes not accounted for by these health states may also influence HRQoL, in particular among patients with less severe types of SMA.[215, 216] For example, factors such as fatigue, respiratory function, endurance and improvements in fine motor movement may influence the ability of an older patient with SMA to perform activities of daily living and to participate in society.[213] Therefore, the clinical benefits associated with earlier intervention may be underestimated.

As noted previously, there is considerable uncertainty associated with key input parameters and assumptions, in particular, utility values, the durability of treatment effects in the long-term and the appropriate treatment strategy for patients with four or more copies of *SMN2* copies. Uncertainty was partially accounted for in sensitivity and scenario analyses, although the true uncertainty may be different to that represented in these analyses, given the uncertainty associated with base case values and assumptions for key outcomes, and that not all relevant parameters were

included in sensitivity analysis. The management of SMA has evolved significantly in recent years, with no licensed disease-modifying treatments available in Europe prior to 2017. As highlighted in chapter 5, while early evidence is promising, published follow-up data are limited to a maximum of five years and there is a lack of head-to-head trials. In the context of rare disease, it may take many years for reliable data to accrue.

To our knowledge, this is the first systematic review evaluating the cost effectiveness of screening for spinal muscular atrophy relative to clinical presentation. Two systematic reviews of the cost effectiveness of treatments for SMA were identified during scoping.[216, 217] Consistent with our findings, Paracha et al. highlighted that inconsistencies in the modelling approach across CUAs presented challenges for drawing comparisons between results of individual studies.[216]

As noted in section 6.3.4, conflicts of interest arising from relationships with pharmaceutical companies were reported in three out of the five included studies. According to a Cochrane review, industry-sponsored studies have been shown to have more favorable efficacy results and conclusions when compared with studies sponsored by other sources. Furthermore, it was reported that these findings cannot be explained by standard risk of bias assessments.[218] This suggests that, in addition to standard methodological quality assessment, careful consideration of funding sources is required in the interpretation of study findings as part of the systematic review process. Of note, researchers at the School of Health and Related Research in the UK are currently undertaking a de novo, modelling study to inform decision-making by the UK National Screening Committee, given limitations in existing economic evaluations.[219] Given the potential for bias related to industry funding in existing studies, this study will be an important contribution to the existing literature. However, it is important to acknowledge that while such a model may go some way towards addressing the potential for industry bias in existing economic evaluations, it will still be subject to the numerous limitations in the existing clinical evidence base, which presents challenges for reliable estimation of long-term cost effectiveness.

6.4.1 Limitations

Despite a robust approach to the systematic review process, including publication of a protocol and adherence to national and international guidelines, the findings of this systematic review should be interpreted with consideration of the limitations of the review process and the underlying evidence base.

Limitations of the underlying clinical evidence include potential concerns regarding the generalisability of study populations, the absence of long-term clinical outcomes, and uncertainty regarding utility values and durability of the treatment effect. In the absence of comparative data, the effectiveness of screening relative to clinical

presentation was based on a naïve indirect comparison of single arm trials. While this approach may be considered reasonable in the absence of comparative data, the results should be interpreted in the context of the limitations of the approach which have the potential to introduce significant bias into estimates of cost effectiveness. Due to difference in baseline clinical characteristics and prognostic factors (for example, age at treatment initiation, disease duration, motor milestones achieved, *SMN2* copy number) outcomes from single arm clinical trials may not be comparable, particularly in the context of limited sample sizes. Nevertheless, such long-term follow-up data will not be available to address the immediate need for decision-making.

There are numerous tools to assess methodologic and or reporting quality of cost effectiveness studies. Guidance from ISPOR suggests that the most appropriate tool for a given review depends on factors such as the research question and available resources.[199] As a pragmatic approach, CHEC-list was used for the purposes of the review as the criteria covered by the tool were considered to offer sufficient coverage of key methodological issues. While the Philip's tool may offer a more thorough assessment of the quality of data sources underlying the model structure,[220] it has been argued that given the number of criteria included, use of this checklist may not be feasible in systematic reviews.[221] As this systematic review includes an assessment of both methodological quality and transferability, the processes used within the review are robust, so that flaws important to the interpretation of the evidence are likely to have been identified.

The evidence base for the cost effectiveness of screening for SMA relative to clinical presentation is limited and subject to substantial uncertainty. While inclusion of conference abstracts may be important in the context of a limited evidence base,[222] for the purposes of this review it was considered unlikely that the level of information provided would be sufficient to facilitate critical appraisal. Moreover, it is recognised that such studies will be largely subject to the same limitations identified in the existing literature, that is, uncertainty as to the proportion of the screened population that will require immediate treatment given the recent implementation of screening in many countries and a lack of long-term treatment effectiveness data. Therefore, conference abstracts were excluded.

This systematic review cannot address the issue of affordability, which may be an important issue given that a proportion of patients may experience late-onset in the absence of screening. The estimated incremental budget impact associated with the potential addition of screening for SMA to the NNBSP is presented in chapter 7.

6.4.2 Conclusion

In the absence of robust clinical data inputs, published economic evaluations adopted diverse approaches to estimating the cost effectiveness of newborn bloodspot screening for SMA relative to clinical presentation, leading to heterogeneous results. The available evidence suggests that the cost effectiveness of newborn bloodspot screening for SMA is highly dependent on the choice of disease-modifying treatment following a positive screening test result. Under the modelled assumptions, treatment strategies including OA were associated with more favourable cost effectiveness estimates when compared with nusinersen. However, the absence of either long-term effectiveness data for these drugs or data from head-to-head trials is noted, so there is substantial uncertainty regarding the assumptions used in this regard. Identified research gaps, including the absence of agreed best practice guidelines for the diagnosis and management of SMA with disease-modifying treatments, the lack of long-term comparative data comparing outcomes of screening with no screening, the lack of evidence for those with higher *SMN2* copy numbers, and the absence of an agreed approach to estimation of utility values, present challenges for all CUAs attempting to estimate the cost effectiveness of newborn bloodspot screening for SMA. At present, there is insufficient evidence to address these identified research gaps in order to inform a reliable estimate of the cost effectiveness of newborn bloodspot screening for SMA in the Irish context.

7 Organisational and budgetary implications

Key points

- This chapter outlines the organisational and budgetary implications associated with the potential addition of spinal muscular atrophy (SMA) to the National Newborn Bloodspot Screening Programme (NNBSP) in Ireland.
- In terms of laboratory considerations, screening for SMA involves the same PCR-based technology as screening for severe combined immunodeficiency (SCID). Therefore, multiplex assays may be used to perform dual screening for these conditions. Should screening for SMA be recommended, this would potentially result in operational efficiencies in terms of the equipment requirements, physical space requirements, and training needs of staff, as compared to a scenario where SMA were to be introduced in the absence of screening for SCID.
    - At least two kits are currently available commercially which allow for multiplex detection of both SMA and SCID.
- Due to infrastructural constraints, implementation of screening by the National Newborn Bloodspot Screening Laboratory is unlikely to be feasible until the new children's hospital on the St James's campus is operational. Appropriate resourcing of the National Newborn Bloodspot Screening Programme is essential for the functioning of the programme as a whole.
- In terms of treatment pathways, the introduction of screening for SMA would change the way in which certain children with SMA are managed. Some cases may receive a different treatment to that which they would have received if they had presented symptomatically at a later point. This would have resource and budget implications for the HSE.
    - In the absence of screening, processes for watchful waiting, including the frequency of follow-up and criteria for treatment initiation, have not been established. If a decision were made to implement screening for SMA, the need for and structure of a watchful waiting strategy would need to be considered.
- Resources may be required for ongoing monitoring of the programme and the outcomes of screening for SMA.

- A budget impact analysis was undertaken to estimate the incremental budget impact associated with the addition of screening for SMA to the NNBSP relative to identification based on clinical suspicion or family history.
- For patients with a diagnosis of SMA, the treatment pathway was determined according to disease type in the current care arm, and survival motor neuron *2 (SMN2)* copy number in the screening cohort.
    - In the current care arm, patients with type I SMA were modelled as being treated with onasemnogene abeparvovec (OA). Patients with types II and III SMA were modelled as being treated with nusinersen or risdiplam.
    - For the purposes of this analysis, in the screened cohort, it was assumed that patients with a homozygous survival motor neuron *1 (SMN1)* deletion and three or fewer copies of *SMN2* would receive immediate treatment with OA. For patients with four or more copies of *SMN2,* it was assumed that treatment would be initiated following symptom onset.
    - The incremental budget impact associated with the addition of screening for SMA to the NNBSP (that is, the budget impact over and above current expenditure in the absence of screening), was estimated at approximately €17.7 million (95% confidence interval (CI): €5.1 to €40.5 million) over a five-year time horizon. This was estimated using publicly known drug list prices.
    - Approximately 90% of these costs relate to drug treatment (€16.3 million, 95% CI: €3.8 to €38.9). Total laboratory costs, comprising equipment and consumables associated with screening, were estimated as representing less than 5% of costs (€0.7 million, 95% CI: €0.6 to €0.8). The costs of scheduled healthcare utilisation (€0.1 million, 95% CI: €0.02 to €0.3) and clinical staff (€0.5 million, 95% CI: €0.4 to €0.7) also comprised a small proportion of costs (less than 5%).
- Given a high level of uncertainty is inherent to research related to rare diseases, extensive sensitivity and scenario analyses were undertaken. These demonstrated a substantial degree of uncertainty around the point estimate, largely attributable to the considerable uncertainty relating to the epidemiological inputs, the cost of disease-modifying treatments (in particular the potential for confidential pricing agreements), and the knowledge gaps related to reimbursement criteria for available disease-modifying treatments.

- It is likely that screening would be associated with an increase in the proportion of patients with SMA treated with OA, relative to current care. As OA is associated with a very high upfront cost, its contribution to the overall budget impact is particularly observed over shorter time horizons (such as the five years modelled). However, use of a longer time horizon would be subject to even greater uncertainty given the evolving treatment landscape

7.1 Introduction

The purpose of this chapter is to consider the organisational and budgetary consequences for the Irish healthcare system associated with the potential addition of screening for spinal muscular atrophy (SMA) to the National Newborn Bloodspot Screening Programme (NNBSP). The potential organisational implications for the NNBSP and the wider healthcare system are discussed in section 7.2. The estimated incremental budget impact analysis (BIA) is presented in section 7.3.

Of note, at a programme level, appropriate resourcing of the NNBSP is essential for the functioning of the programme as a whole. However, the scope of this chapter is limited to the additional organisational and budgetary resources that would be required to implement screening for SMA specifically. In January 2023, the Minister for Health approved a recommendation by the National Screening Advisory Committee (NSAC) to add screening for severe combined immunodeficiency (SCID) to the NNBSP.[223] During consultation with the National Newborn Bloodspot Screening Laboratory (NNBSL), it was identified that SMA and SCID can be detected using the same screening kit and testing methodologies. Therefore, given the planned implementation of screening for SCID, only additional resources required to implement screening for SMA as part of the NNBSP, which are beyond those required for the SCID, were considered in this HTA.

In terms of the addition of SMA where SCID has already been recommended, this potentially produces synergies in terms of pre-analytical (for example, education and training, and procurement) and analytical stages (for example, laboratory resource consumption), as compared to a scenario where SMA were to be introduced in the absence of screening for SCID.

7.2 Organisational considerations

This section considers the organisational implications associated with the potential addition of screening for SMA to the NNBSP, and has been guided by the assessment elements outlined in the EUnetHTA Core Model 'Organisational aspects' domain.[224]

These potential organisational implications relate to changes to NNBSP current practice, laboratory considerations, clinical pathways, follow-up capacity, and acceptability of the programme (a performance metric). 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.[157]

As a number of organisational implications that are common to any new addition to the NNBSP have been covered in detail in a previous HIQA HTA of the addition of screening for SCID to the NNBSP, they will not be repeated in the present HTA.[10] These include:

- sample collection
- updating of NNBSP resources, parent and sample-taker information
- decision-making regarding buying or leasing laboratory equipment
- quality assurance and evaluation
- addition of future newborn bloodspot conditions.

Furthermore, given screening for SMA uses the same technology as screening for SCID, there will be commonalities in the organisational implications for the addition of both conditions. These commonalities are addressed briefly, but again have been covered in detail in the previous HIQA HTA (link).[10]

7.2.1 Changes to current NNBSP practice

Beyond the common changes with the addition of any condition to the programme, it is not anticipated that the addition of screening for SMA would result in any specific change to NNBSP practice. It was highlighted by the NNBSP Governance Group that, with the exception of the laboratory staffing identified below, that the NNBSP itself was unlikely to require additional staff (for example, clinical or administrative staff) if screening for SMA were to be implemented, provided the current requirements submitted as per the HSE National Service Plan for 2024 are fulfilled.[86]

Informed consent

As with the addition of any new condition to the NNBSP there would be a need to update material and processes associated with informed consent for testing. Screening for SMA involves the testing of genetic material. Genetic data contain sensitive health and non-health-related information about an individual and their family. Therefore, adopting adequate privacy safeguards is important when processing genetic data for research or clinical purposes.[225] The outcomes of a genetic test can have implications at an individual or familial level, for example, cascade testing of family members or the potential influence on family planning decisions. Therefore, ensuring a sufficiently informed consent process for all possible contingencies is challenging to achieve.[226] It is important that the implications of screening using genetic material are considered in the context of the General Data Protection Regulation (for example, Recital 34 – Genetic data), which entered into

force in May 2016.[227] Under this regulation, genetic data are considered a special category of sensitive personal data, and are subject to robust safeguards. It is therefore important that parents or guardians are provided with sufficient information to make an informed decision.

7.2.2 Laboratory considerations

Screening for SMA involves the same polymerase chain reaction (PCR)-based technology as screening for SCID and multiplex assays are available which allow for the dual detection of these two conditions. It is anticipated that, should screening for SMA be recommended, this will be associated with operational efficiencies from a laboratory perspective in terms of the equipment requirements, physical space requirements, and the training needs of staff, as compared to a scenario where SMA were to be introduced in the absence of screening for SCID.[10, 86] In terms of training needs specifically, given this form of technology is new to the NNBSL, it was highlighted that a training visit to a European laboratory who are experienced in this form of screening to identify best practice may be beneficial for staff members.[86]

As per the considerations outlined in the previous HIQA HTA of T-cell receptor excision circles (TREC)-based screening for SCID, the verification and implementation of this form of screening will be impacted by the planned move to the new children's hospital on the St James's Hospital Dublin campus.[10] It is not anticipated that such verification processes could begin prior to the laboratory at the new children's hospital being operational.[86]

Staffing requirements

In the context of this HTA 'verification' is defined as the precursor processes of establishing the testing method (for example, definition of cut-offs relative to population norms) whereas 'implementation' refers to the day-to-day screening of samples once the condition is formally added to the NNBSP.

The NNBSL noted that, should screening for SMA be recommended, verification and implementation of the testing methods for SMA and SCID screening could take place concurrently. Therefore, no additional laboratory staff would be required for the verification or implementation phases, under the assumption that staff requirements submitted as part of the HSE National Service Plan to implement TREC-based screening for SCID are met.[86]

Additionally, while not specific to screening for SMA, it was highlighted that there is a requirement for a Clinical Liaison Officer to facilitate the efficient running of the NNBSP. This requirement has been submitted for consideration as part of the HSE 2024 National Service Plan and has, therefore, not been costed within this HTA.

Equipment and consumables

In order to expand the current laboratory testing capacity of the NNBSL, additional equipment and consumables would be required should screening for SMA be recommended. The type, quantity and cost of such equipment and consumables were estimated in consultation with the NNBSL, and are outlined in section 7.3, Table 7.2. Of note, estimation of the incremental equipment requirements needed to facilitate the addition of SMA to the NNBSP is challenging, given that screening for SCID is not yet in place, in addition to other organisational uncertainties. It is possible that amendments to the proposed requirements for equipment and consumables will be needed based on identified needs during the verification and early implementation stages, the potential for disruptive innovations (for example, changes to the information and communication technology (ICT) interface, or new CE-marked test kits) and ongoing uncertainties associated with the move to the new children's hospital.

As noted previously, multiple assays are available which permit dual detection of SMA and SCID. Up to the time of writing, at least two such kits are available commercially, namely, the PerkinElmer EONIS™ platform, and the Immuno IVD SPOT-it™ screening kit.[37, 38] Both manufacturers note that the assays are CE-marked (that is, that a product meets requirements for sale in the EEA).[37, 38] Should screening for SMA be recommended, a decision regarding which test kit is used would be dependent on the outcome of a formal tendering process. Such a decision may involve the trialling of different kits and a comparison of test accuracy relative to population norms.[86]

Second-tier testing

As outlined in chapter 4 (clinical effectiveness of screening) there is variation internationally in the use of second-tier testing for SMA screening. The introduction of a second tier of testing can be used to confirm homozygous deletion in the survival motor neuron 1 (*SMN1)* gene and to quantify survival motor neuron 2 (*SMN2)* copy number therefore facilitating a diagnosis of SMA. It may be possible for second-tier testing to be undertaken using the original dried bloodspot sample taken for the purposes of newborn screening. Alternatively, following an abnormal screening test result, the newborn and their parent(s)/guardian(s) would be requested to present in the outpatient setting for a blood draw. Performing confirmatory testing on the original dried bloodspot sample would likely result in efficiencies for the referral pathway and faster turnaround times (as outlined in section 7.2.3 below).[86] However, a decision on the most appropriate sample for second tier testing would be dependent on the outcomes of the laboratory verification process prior to implementation.

A decision would be required on the location of such second-tier testing, should screening be implemented. It was highlighted that the Molecular Genetics Laboratory at Children's Health Ireland (CHI) Crumlin has organisational advantages given this laboratory is already equipped for SMA diagnostic and carrier testing using MLPA technology; however, there is the possibility of establishing the testing method within the NNBSL.(86) The appropriate site of implementation would likely be informed by the outcomes of verification of the testing method in the Irish context, in particular, the expected number of false positive results. A decision to implement confirmatory testing at the NNBSL would be associated with additional equipment, consumables, and space requirements. The expected test turnaround time at each possible location is an important consideration, given the potential for rapid and irreversible loss of motor neurons.

For cases with a positive screening test result, cascade testing of parents is typically undertaken to determine carrier status; where clinically indicated, cascade testing of siblings may also be performed. Other adult relatives often also present for carrier testing once an index case had been diagnosed genetically in a family. It is anticipated that there would be sufficient capacity in the Molecular Genetics Laboratory at CHI Crumlin to conduct cascade testing in addition to the capacity required for second-tier testing of screen positive cases. As discussed in chapter 3, the true epidemiology of SMA in Ireland is uncertain, as available estimates only reflect the proportion of patients that have presented clinically, or were identified based on sibling diagnosis. There is potential for increased demand for diagnostic testing, relative to current practice, due to the identification of all SMA cases across the disease spectrum.

It is noted that digital droplet PCR (ddPCR) has been used to conduct diagnostic testing in some laboratories internationally due to the potential for operational efficiencies and technical advantages (for example, less sensitive to PCR inhibitors and no requirement for a standard curve to quantify *SMN2* copy number).(228) For example, in the Australian context, the newborn bloodspot screening laboratory obtained accreditation for *SMN2* testing with ddPCR on dried bloodspot samples to mitigate issues associated with reduced testing capacity during the COVID-19 pandemic.(81) For the purposes of this HTA, it was assumed that confirmatory testing would be carried out using multiplex ligation-dependent probe amplification (MLPA), as this is the reference standard and the current method used by the Molecular Genetics Laboratory at CHI Crumlin. As outlined in scenario analysis in the BIA, adoption of ddPCR in the Irish context would require a significant upfront investment.

Definition of screen positive cases

As highlighted in chapters 2 (description of technology) and 4 (clinical effectiveness of screening), there is some variation in the definition of screen positive cases internationally. The diagnostic definition of SMA is bi-allelic disruption in the *SMN1* gene,[1] and this has been used to define screen positive cases in the majority of programmes implemented internationally to date. However, in Sweden and Canada (provinces of Alberta, British Columbia, Manitoba, and Ontario) a criterion for screen positivity based on *SMN2* copy number has been introduced such that cases with higher copy numbers (those above three and four *SMN2* copies, respectively) are not reported as screen positive.[42, 43, 139] It is important to note that such decisions were linked to the reimbursement criteria for disease-modifying treatments in these countries and uncertainty in the disease course.[42, 47] Important considerations underpinning the definition of screen positivity applied in a given context are outlined from an ethical perspective in section 8.3.4, and discussed further in section 9.4. From an organisational standpoint, if a decision were made to define screen positivity based on *SMN2* copy number (as opposed to solely on the basis of homozygous deletion of *SMN1*), this would directly impact the total number of positive cases being reported by the NNBSP and may have implications for the management of certain cases with higher copy numbers.

Information and communication technology considerations

As with any new condition, the addition of SMA to the NNBSP would require updates to the laboratory ICT system. While not specific to screening for SMA, it was highlighted that there are currently significant ICT infrastructure issues being experienced by the NNBSL with these issues having the potential to impact on the addition of any new conditions to the NNBSP.[86] These include the need for a new server to host the Laboratory Information Management System (SpecimenGate®) and connectivity issues. In particular, SpecimenGate® is currently in use at the NNBSL to manage samples as they navigate through the testing workflow (for example, storing test results and quality control). This software was primarily designed to interface with PerkinElmer instruments. The compatibility of the test kit with existing ICT infrastructure would be an important consideration if a decision were made to implement screening or SMA.

7.2.3 Clinical pathways

There are a number of considerations relating to clinical pathways in the context of the introduction of screening for SMA. These may be considered in terms of the referral pathway and the treatment pathway.

Importantly, if a decision were made to introduce newborn screening for SMA, cases born prior to the introduction of screening would continue to present clinically with symptoms in the long-term due to the broad variation in age at symptom onset (ranging from early childhood to adulthood). Therefore, current referral pathways for patients presenting clinically with symptoms would need to remain in place.

Referral pathway

As outlined above, decision-making regarding whether or not to introduce second-tier testing would influence the referral pathway. As noted previously, it is anticipated that the use of this tier would involve the same dried bloodspot sample and immediate referral to a paediatric neurologist following a positive result.[86] In the absence of a second-tier test using the dried bloodspot sample, the child and their caregiver may be required to attend an appointment for a blood draw which would then be sent for confirmatory testing. Under the current care, diagnostic testing for SMA takes place in CHI Crumlin or through an external provider in Germany. Following confirmation of SMA through diagnostic testing, timely referral to a paediatric neurologist is important to initiate the appropriate treatment pathway. This is particularly relevant for more severe SMA types for whom the latency period before symptom onset may be very short (as outlined in chapter 4: clinical effectiveness).

Management pathways

In the context of newborn screening for SMA, decision-making regarding treatment access would likely be made on the basis of *SMN2* copy number and, for the majority of cases, in the absence of a known SMA type (as SMA type is related to symptomatic presentation, the majority of cases of SMA detected through newborn screening would be expected to be asymptomatic at the time of testing). As noted throughout this HTA, while copy number is generally inversely associated with disease severity, this is not absolute and discordant cases do present.[2, 22] The introduction of screening for SMA would likely change the approach to treatment of patients of SMA, with some patients accessing an alternative treatment pathway than they would have received if they had presented symptomatically at a later point. This would have resource and budget implications for the HSE. A potential treatment pathway has been outlined in chapter 2 (description of technology) which has been used as the basis for this HTA. Additionally, as further evidence and new disease-modifying treatments emerge, and as licensing and reimbursement criteria are refined, treatment pathways may be updated.

In the current context of SMA treatment, the decision to treat with OA is dependent on the current reimbursement criteria as well as the patient's status with regard to the presence or absence of anti- adeno-associated virus 9 (AAV9)-binding antibody

titres, as described in chapter 5 (overview of treatments). In the context of screening, similarly, for patients considered for treatment with OA there would be a requirement for testing for the presence of anti-AAV9 antibodies prior to infusion. In collaboration with the manufacturer of OA, centralised testing for elevated anti-AAV-9 titres is currently conducted in a single laboratory in the Netherlands with the cost for all such testing incorporated into the drug price. If screening for SMA were to be introduced, it is anticipated that testing would continue to be delivered at this site at no additional cost.[86] In the event that anti-AAV9-binding antibody testing for anti-AAV-9 antibodies could no longer be conducted at this site, testing would need to be arranged at an alternative site with an acceptable turnaround time and appropriate quality assurance processes. This would potentially be associated with additional costs.

Should screening be implemented, a watchful waiting strategy may be adopted for a small proportion of patients estimated to be at lower risk of disease progression. It is anticipated that patients would be monitored for clinical signs and symptoms, including monitoring using nerve conduction studies, more frequently in the first year of life (for example, every three months) to exclude the potential for type I SMA. Thereafter, the frequency of monitoring could be reduced (for example, a reduction to every six months), but this frequency may vary depending on individual patient needs. A structured and balanced approach to monitoring would need to be determined to ensure an appropriate balance between identification of clinical signs and symptoms at the earliest possible point, efficient use of healthcare resources, and minimising the burden on patients and caregivers associated with attending healthcare appointments. Decision-making would also be required regarding the trigger for provision of treatment (for example, a decision to treat upon onset of subtle, subclinical neurophysiological changes versus treatment only upon manifestation of symptoms).

7.2.4 Follow-up capacity

A number of additional capacity considerations were identified within this HTA as relevant; these relate to capacity for second-tier, or, depending on the approach taken, confirmatory testing, and capacity for clinical appointments.

If screening is introduced, it is not anticipated that additional laboratory staff would be required to facilitate second-tier testing should this be implemented in the Molecular Genetics Laboratory at CHI Crumlin. However, this assumption is based on the findings of chapters 3 (epidemiology) and 4 (clinical effectiveness) in relation to the expected volume of SMA cases and false positives as reported in the literature.[86] Should the observed numbers in the real world setting of screening exceed those estimated based on literature findings, then it is likely that additional staffing would be required.

With respect to hospital-based SMA services, a number of requirements and resource concerns were highlighted. Considering available psychology services, it was noted that an additional WTE clinical psychologist would be required to provide psychological support to patients and their families should screening be introduced. Additional consideration would also need to be given to allocation and timing of existing resources for genetic counselling. If screening were to be introduced, this would lead to a change in timing of presentation, where cases are identified shortly after birth. Families may require access to genetic counselling, including educational support, at that time.[155] Furthermore, it was highlighted that there are existing identified resource deficits in the neuromuscular service that supports children with SMA, including physiotherapy, occupational therapy, dietetics, and speech and language therapy services. The importance of addressing these resource needs was emphasised both to optimise the evolving care needs of patients with SMA and in light of the potential for increased demands on services associated with earlier diagnosis.

As highlighted in chapter 3 (epidemiology), while it is likely that the majority, if not all, cases of SMA identified through screening would present clinically at some point, the age of clinical presentation can be wide-ranging depending on the SMA type. In the context of newborn screening, all cases associated with a homozygous deletion of *SMN1* would be expected to be identified in infancy through screening. This may have implications for clinical appointment capacity given that cases, whether treated or not, would require access to care and monitoring earlier than would occur in the absence of screening. Furthermore, given some cases of SMA born in recent years will not present symptomatically until later childhood and adolescence, under a scenario of screening being in place, patients will continue to present clinically with symptoms and require access to diagnostic testing and treatment after screening is implemented. Clinical presentation would also continue to potentially include children who did not have the opportunity to avail of newborn screening despite its implementation (for example, children who migrate to Ireland after infancy having not undergone newborn screening abroad). While recognising that no treatments are currently available for those where the need for treatment initiation is identified after the age of 18 years, clinical handover to adult neurology services will be required for those following a watchful waiting strategy, potentially increasing demand on such services. 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.

7.2.5 Acceptability

The acceptability of a screening programme is an integral consideration within decision-making, as evidenced by criteria set out by Wilson and Junger,[229] the

World Health Organization (WHO),[230] and the NSAC in Ireland specifically.[231] 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%.[232] The notably high uptake rate of the current NNBSP indicates near population-wide coverage;[232] therefore, any potential harm to the trust and confidence in the NNBSP as a result of the introduction of screening for SMA, alongside any other conditions added in the future, should be considered. 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.[230]

In terms of SMA specifically, uptake rates of programmes internationally outlined in chapter 4 (clinical effectiveness) were generally noted to be acceptable, though one US study from Massachusetts that required specific consent for SMA screening separate to newborn screening generally noted lower rates of uptake compared with previous state-wide implementations (85% versus 98%).[135] Furthermore, a Japanese pilot study which had a notably lower uptake rate relative to other studies of 22% with the authors hypothesising that willingness to participate may have been impacted by parents' lack of awareness of the seriousness of the condition and the availability of pre-symptomatic treatment options.[147] A 2018 study of the general population in the UK, found that 84% (n = 196) would support newborn bloodspot screening for SMA.[233] It should be noted that this survey was completed prior to availability of disease-modifying treatments beyond clinical trials.

7.2.6 Quality assurance

With consideration to key areas of uncertainty, in particular the epidemiology of SMA types in Ireland, the risk-benefit balance for some subgroups, and the lack of long-term effectiveness data, ongoing monitoring of programme outcomes would be of critical importance, if a decision were made to introduce screening for SMA. The NNBSP has an established quality assurance programme. Consistent with existing processes, the NNBSP governance group would be responsible for coordinating a quality assurance programme, against an agreed set of quality assurance criteria.[234] Consideration is required to be given to resources needed for ongoing monitoring of the programme and outcomes of screening for SMA.

7.3 Budget impact analysis

A BIA was undertaken to estimate the incremental budget impact associated with the addition of screening for SMA to the NNBSP relative to identification based on clinical suspicion or family history.

7.3.1 Methods

The BIA was conducted in accordance with the HIQA guidelines for budget impact analysis and economic evaluation in Ireland,[200, 235] and performed using Excel 2013. The model follows an open cohort structure where new patients enter the model each year.

It is important to note that, consistent with best practice recommendations, a conservative approach was adopted, from the perspective of the budget holder, in circumstances where assumptions were necessary due to limitations in the evidence base (that is, the maximum plausible cost was assumed). A list of model assumptions and justifications is presented in Supplementary Appendix Chapter 7, Table A7.1.

Target population

The target population for the BIA was 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 average projected births between 2024 and 2033.[236] The uptake rate for screening was assumed to be 99.9%, consistent with the current uptake rate for newborn screening.

The target condition was SMA. For the purposes of this analysis, it was assumed that all cases with a homozygous deletion of *SMN1*, irrespective of *SMN2* copy number, would be considered 'screen positive', and enter the clinical pathway.

Perspective and time horizon

The BIA estimated the incremental cost associated with the addition of screening for SMA to the NNBSP over a five-year time horizon.

The analysis adopted the perspective of the Irish publicly-funded health and social care system, namely the Health Service Executive (HSE). Accordingly, only direct costs to the HSE were considered. Indirect costs such as productivity losses associated for those with SMA and for caregivers of those with SMA, and out-of-pocket expenses incurred by individuals and their families attending appointments, were excluded from the analysis, but are considered in section 7.4.

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 100 hours after birth. The blood sample is

processed to detect nine rare, but serious health conditions (chapter 2, section 2.1). This HTA considers the addition of SMA to the current NNBSP in Ireland.

The comparator for this BIA is current practice for detection of patients with SMA, that is, identification based on clinical suspicion or family history.

Treatment pathway

As described in chapter 5 (overview of treatments), at present, three drugs have been licensed by the European Medicines Agency (EMA) for use in the European Union to treat SMA: onasemnogene abeparvovec (OA) (Zolgensma®), nusinersen (Spinraza®) and risdiplam (Evrysdi®). These drugs differ in their licenced indications, administration requirements (for example, frequency and setting) and reimbursement criteria. For the purposes of this analysis, treatment options for individual disease types were modelled based on assumptions relating to current reimbursement criteria, the licenced indications and relevant published economic evaluations, as described below. As noted in chapter 5, current HSE reimbursement criteria were established in the absence of potential screening for SMA. Reimbursement criteria may differ in the event that screening for SMA is introduced.

The treatment pathway modelled in the current care and screening arms is presented in Figure 7.1. In both cohorts, following a diagnosis of SMA, treatment was modelled as initiating in accordance with current reimbursement criteria as part of a shared decision-making process.

Nusinersen, risdiplam and OA are currently reimbursed for patients with type I SMA (chapter 5, Table 5.2). In the current care cohort it was assumed that patients presenting with type I SMA would receive one-off treatment with OA, in part due to the likely preference for one-off treatment. For the purposes of the model, it was assumed that patients presenting with types II and III SMA would receive nusinersen or risdiplam, and would require ongoing maintenance dosing.

The costs of managing patients with types 0 and IV SMA were not included in the current care cohort. With respect to type 0, the cost of managing cases is equivalent in the current care and screening cohorts as these patients are managed with supportive care due to the severe nature of the disease at the time of birth. Management costs associated with type IV SMA were considered to be beyond the scope of this budget impact analysis (that is, five-year time horizon), given that these patients will not present until at least 18 years of age in the current care cohort.

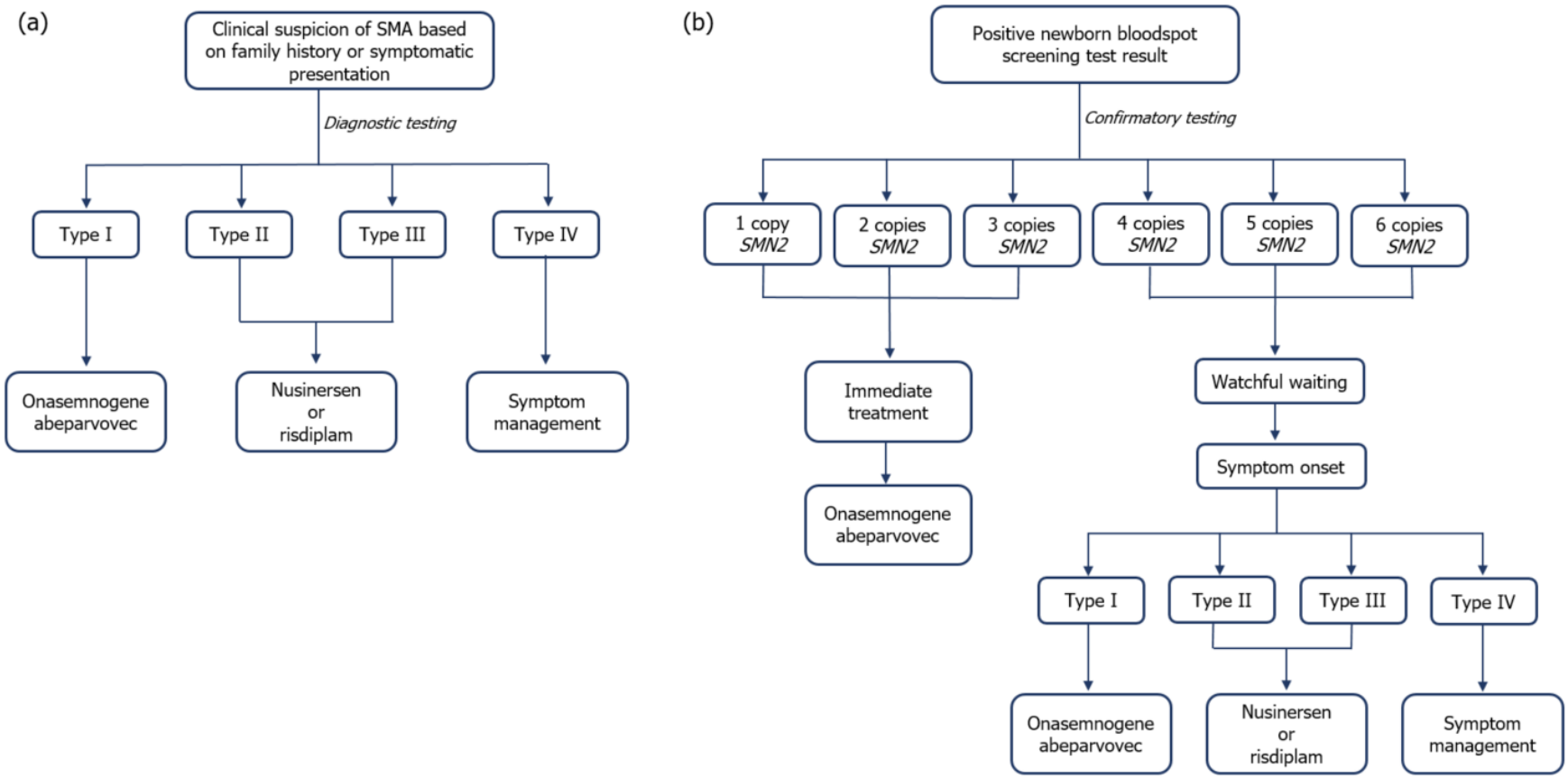
In the screening cohort, it was assumed that the parent(s) or legal guardian(s) of infants with a confirmed diagnosis of SMA would be contacted and clinical pathways initiated based on the SMA genotype detected. Based on a possible Irish treatment

pathway outlined by Irish clinical specialists, it was assumed that all patients with three or fewer copies of *SMN2* would be managed with OA (chapter 2, section 2.3.3). With consideration to available epidemiological estimates, and, assuming current reimbursement criteria hold in the context of screening, it is likely that screening would be associated with an increase in the proportion of patients with SMA receiving OA, relative to current care. For presymptomatic patients with four or more copies of *SMN2,* the possible pathway outlined by clinical specialists, presented in section 2.3.3, suggests a watchful waiting strategy. Of note, if a decision is made to implement screening for SMA, the clinical care pathway may differ depending on the available evidence for treatment effectiveness and access arrangements at the time of implementation. Therefore, for these patients, treatment was modelled as being initiated following symptom onset in accordance with the diagnosed SMA type (for example, symptomatic presentation at 18 months to three years of age would be considered type IIIa SMA). Treatment options for patients presenting clinically with four or more copies of *SMN2* were modelled as being consistent with treatment options available as part of current care.

In both cohorts, although long-term follow-up data are lacking, it was assumed that no patients would discontinue treatment; this was based on available local data and evidence from clinical trials at the time of analysis. In the base case analysis it was assumed that nusinersen and risdiplam would be prescribed in equal proportions.

While *SMN2* copy number is the major known disease modifier, its prognostic value is not absolute (for example, some patients with two *SMN2* copies present with a milder SMA type, whereas others with three copies present with a more severe type). Therefore, for the screened cohort, it is not possible to predict disease phenotype with certainty. As a result, the relative proportions of patients receiving each type of disease-modifying treatment differ between the screening and current care arms.

Figure 7.1 Schematic presentation of the assumed treatment pathways within this analysis for the SMA cohorts of (a) current care and (b) newborn bloodspot screening.



Key: SMA – spinal muscular atrophy; *SMN* - survival motor neuron.
Type III SMA can be further subdivided into types IIIa (18 months to three years of age) and IIIb (three to 18 years of age). Patients with type IV SMA present in adulthood. Therefore, not all types shown will present within the time horizon of this analysis (5 years). All types are shown for completeness. As noted, the depicted treatment pathways are based, in part, on assumptions relating to current reimbursement pathways, developed in the absence of screening. Should screening be implemented, treatment reimbursement and treatment clinical pathways may differ.

Input parameters

Testing outcomes

Based on the evidence presented in chapter 4, screening for SMA is highly accurate for the identification of *SMN1* deletion in exon 7. Therefore, the number of positive screens was assumed to be consistent with the observed incidence based on national and international estimates (described in the following section). It was estimated that approximately 60,000 screening tests would be conducted per year to account for uncertainty in the birth rate, and the potential for repeat testing due to inconclusive results, sample contamination or deterioration, or quality issues related to the sample and/or dried bloodspot (DBS) card (for example, sample collected too early, damaged, or incomplete DBS card).

Due to limitations in the testing methodology, it was assumed that 2 to 5% of incident cases with compound heterozygous variants would not be identified by the screening test.

Epidemiological outcomes

Given the rarity of the condition, and the small annual birth cohort in Ireland, available national epidemiological data sources are associated with considerable uncertainty. Therefore, epidemiological estimates were based on the international literature (chapter 3), and were corroborated by national data sources, where available, and by expert clinical input. As discussed in chapter 3, these estimates represent the best available evidence at the time of analysis, however they are subject to considerable uncertainty related to the quality and completeness of the data.

The incidence of SMA was estimated to be 11.9 per 100,000 (ranging from 6.3 to 25.5 per 100,000; chapter 3) based on a secondary analysis of international epidemiological estimates. In absolute numbers, this represents a range of two to 13 cases per annum, based on the estimated annual birth cohort size of 58,000. These data are broadly in line with national epidemiological estimates with consideration to naturally occurring variation in the context of rare diseases and the potential for underdiagnosis of milder disease types.

In the current care arm, it was estimated that cases with type I SMA would comprise more than half of all diagnosed SMA cases, based on a secondary analysis of data presented in a published review (Table 7.1).[21] Patients with type II and III SMA comprised 24% and 21% of all diagnosed SMA cases, respectively. As described in chapter 3, the age of onset for type III SMA is highly variable, ranging from three to 18 years. Based on the available evidence, it was assumed that approximately half of patients with type III SMA would present between 18 months and three years

(that is, type IIIa SMA) and half would present between three and 18 years (that is, type IIIb SMA).[22]

In the screening arm, a secondary analysis of two published reviews (chapter 3, section 3.3) was used to inform epidemiological input parameters with the aim of estimating:[21, 22]

- Among patients with homozygous *SMN1* deletion, the relative proportion of cases with a diagnosis of SMA categorised by *SMN2* copy number (ranging from one *SMN2* copy to six *SMN2* copies).
- The likely clinical course for patients with four or more *SMN2* copy numbers (that is, SMA type in the absence of presymptomatic treatment). This was estimated in order to inform timing of treatment initiation, if appropriate.

Firstly, it was estimated that 85% of cases identified through screening would have three or fewer copies of *SMN2*, and would therefore be eligible for treatment with OA. The remaining 15% of cases were estimated to have four or more copies of *SMN2* (Table 7.1).

Secondly, the likely clinical course for patients with four or more *SMN2* copy numbers was informed by the distribution of SMA type within the categories of four, five, and six *SMN2* copy numbers. For example, 81% of patients with four *SMN2* copies were estimated to present with type III SMA.

Results of a retrospective chart review and survey of all active SMA patients attending the SMA treatment centre at CHI from 2007 to 2021 suggest that the existing diagnostic pathway for SMA in Ireland can be associated with a prolonged interval between symptom onset and clinical diagnosis.[6] Therefore, it was assumed that screening for SMA would result in faster access to treatment following symptom onset for patients with four or more *SMN2* copies. In the current care arm, available international estimates for age at diagnosis were used to estimate the timing of treatment initiation (Table 7.1).[96] In the screened cohort, for patients with four or more *SMN2* copies, it was assumed that treatment would be initiated at the time of recognised symptom onset (Table 7.1).[96] The range of possible values for timing of treatment initiation were used to inform the staggered presentation of clinical cases over time in the current care arm, and for patients with four or more copies of *SMN2* in the screened cohort.

Table 7.1 Epidemiological data

Parameter	Estimate	Uncertainty	Source
Incidence of SMA per 100,000	11.9	6.3 to 25.5	Secondary analysis of Verhaart et al.[21]
Proportion of SMA cases identified by NBS screening	0.97	0.95 to 0.98	Chapter 3
Proportion of total type III SMA patients with type IIIa SMA	0.54	0.44 to 0.63	Secondary analysis of Calucho 2018[22]
Proportion of total type III SMA patients with type IIIb SMA	0.46	0.37 to 0.56	Secondary analysis of Calucho 2018[22]
Current care arm			
Proportion of patients with type I SMA	0.55	0.45 to 0.68	Secondary analysis of Verhaart 2017[21]
Proportion of patients with type II SMA	0.23	0.19 to 0.25	Secondary analysis of Verhaart 2017[21]
Proportion of patients with type III SMA	0.20	0.12 to 0.27	Secondary analysis of Verhaart 2017[21]
Timing of treatment initiation for type I SMA	5 months	2 to 8	Pera 2020[96]
Timing of treatment initiation for type II SMA	16 months	10 to 22	Pera 2020[96]
Timing of treatment initiation for type IIIa SMA	32 months	27 to 39	Pera 2020[96]
Timing of treatment initiation for type IIIb SMA	118 months	70 to 166	Pera 2020[96]
Screening arm			
Proportion of cases with 1 to 3 *SMN2* copies (treated with OA)	0.85	0.65 to 0.95	Secondary analysis of Calucho 2018[22]
Proportion of cases with ≥4 *SMN2* copies (watchful waiting)	0.15	0.05 to 0.35	Secondary analysis of Calucho 2018[22]
Timing of treatment initiation for type I SMA (≥4 *SMN2* copies)	3 months	1 to 5	Pera 2020[96]
Timing of treatment initiation for type II SMA (≥4 *SMN2* copies)	10 months	6 to 14	Pera 2020[96]

Parameter	Estimate	Uncertainty	Source
Timing of treatment initiation for type IIIa SMA (≥4 *SMN2* copies)	18 months	14 to 22	Pera 2020[96]
Timing of treatment initiation for type IIIb SMA (≥4 *SMN2* copies)	85 months	47 to 123	Pera 2020[96]

Key: CI – confidence interval; NA – not applicable; NBS – newborn bloodspot screening; OA – onasemnogene abeparvovec; PPV - positive predictive value; SMA – spinal muscular atrophy.

Clinical outcomes

This analysis was limited to estimation of the incremental budget impact, for the screened cohort relative to current care, associated with scheduled care costs related to clinical assessment, providing treatment and monitoring treatment outcomes.

Costs

Where appropriate, healthcare costs were adjusted using consumer price indices (CPI) for health and purchasing power parities (PPP) to the latest cost year for which complete data are available (2022), in line with national HTA guidelines for the conduct of budget impact analysis.[235] The cost of goods and services presented is inclusive of value added tax (VAT), at the standard (23%) or reduced (13.5%) rate, as appropriate.[237]

The additional laboratory equipment and consumables required to add screening for SMA to the NNBSP are outlined in Table 7.2. The annual maintenance fee for laboratory equipment was estimated to be 10% of the original purchase price and was applied from year two. Maintenance services were subject to VAT at the reduced rate.[238] Public contracts whose monetary value exceeds €25,000 are subject to a formal tendering process prior to procurement.[239] It is challenging to estimate the cost of such leasing agreements prior to tender. In the absence of reliable estimates of leasing costs, equipment and ICT infrastructure (that is, information and communications technology) costs were recorded as upfront investments.

As noted previously, a multiplex PCR newborn screening assay can be used to simultaneously identify SMA and SCID. Based on consultation with the NNBSP, verification of the testing method for SMA and SCID screening would take place concurrently. Therefore, as noted previously, it is anticipated that additional laboratory staff would not be required for verification of test performance. Based on consultation with the NNBSP, it was estimated that up to 10 multiplex test kits would be required for verification of the testing method. The potential for test kits from more than one manufacturer to be trialled during verification to ensure optimal outcomes of screening (for example, maximise true positives, and minimise false positives, contamination issues and requirements for repeat testing) was accounted for. The incremental cost of accommodating the addition of SMA to the screening panel, in addition to SCID (previously estimated at approximately €5 per test) was estimated to be €2 per test.[10]

In the base case analysis, the site for implementation of second-tier testing was assumed to be the Molecular Genetics Laboratory at CHI Crumlin, given the

availability of the relevant equipment and expertise at this site. It was anticipated that second-tier testing could be completed within existing capacity at CHI Crumlin based on the expected false positive rate (see Appendix Chapter 7, Table A7.1). If the number of false positive results were to exceed the capacity of the Molecular Genetics Laboratory at CHI Crumlin, as an alternative approach, additional equipment would be required to establish second-tier testing at the NNBSL. This was explored in scenario analysis. For the purposes of the BIA, based on consultation with the NNBSL, it was assumed that confirmatory testing could be performed on the original dried bloodspot. However, in practice, operationalisation of the pathway would be dependent on the outcomes of the verification process, as outlined in section 7.2.2.

Based on consultation with clinical experts, it is anticipated that additional inpatient, day case and outpatient care associated with management, treatment administration and outcome monitoring could largely be provided within existing clinical capacity at CHI at Temple Street and St James's Hospital, Dublin. As per section 7.2.4, it was estimated that an additional WTE clinical psychologist would be required to provide psychological support to patients and their families (Table 7.3). All other healthcare utilisation costs were presented as opportunity costs (that is, the cost of healthcare utilisation that is foregone as a result of introducing the new intervention; Table 7.4).

Potential cost offsets through avoidance of unnecessary additional investigations and healthcare visits across specialties were estimated based on a retrospective chart review and survey of Irish patients with a diagnosis of SMA who attended the SMA treatment centre at CHI between 2007 and 2021.[6] In the current care arm, patients were estimated to require 4.9 healthcare visits prior to diagnosis, based on a weighted average of survey responses.[6] The healthcare setting was unclear. As a conservative approach, appointments were assumed to occur in the outpatient setting.

In the screening arm, it was assumed that patients with four or more copies of *SMN2* identified through screening would be monitored three times per year as part of a watchful-waiting strategy. At the point of clinical presentation, patients managed by watchful waiting transfer to the appropriate treatment strategy, depending on the disease type. In clinical practice the frequency of appointments to monitor for signs or symptoms or clinical progression would likely depend on the individual clinical case (for example, follow up at three month intervals for first year to rule out type I, and at six monthly intervals thereafter). For the purposes of this analysis, as a conservative approach, it was assumed that all patients would be monitored three times per annum until clinical presentation.

In Ireland, the cost of inpatient care is recorded in the Hospital Inpatient Enquiry (HIPE) system according to Diagnosis related Groups (DRG).[240] DRGs are designated to group cases which are clinically similar. The estimated cost of daycase and inpatient care for patients treated with nusinersen and OA, respectively, were based on the 2023 Activity Based Funding Admitted Patient Price List.[240] In the absence of DRG codes specific to SMA, codes related to diseases and disorders of the nervous or musculoskeletal system were selected as indicative costs.

In accordance with the clinical care pathway outlined in chapter 2, patients eligible for OA are admitted as inpatients for administration of the gene therapy (Table 7.4). Following discharge, it was assumed that patients would require, on average, eight (range: four to 12) outpatient appointments during the first two to three months post-treatment. Thereafter, patients would require an outpatient appointment for outcome monitoring every four to six months. In the context of the very recent reimbursement of risdiplam in Ireland (September 2023),[173] a clinical care pathway for patients managed with this drug has not yet been established to inform estimation of scheduled care needs). For the purposes of this BIA, it was assumed that the frequency and setting of monitoring for patients treated with risdiplam would be the same as that for patients treated with OA.

As described in chapter 2, patients are admitted as a daycase for intrathecal administration of nusinersen. It was assumed that patients would receive four to six doses of nusinersen in the first calendar year of the BIA, depending on the timing of diagnosis. Thereafter, patients would be admitted as a daycase for administration of maintenance doses three times per annum. It is anticipated that maintenance dosing and outcome monitoring would occur during the same daycase appointment.

Table 7.2 Cost of set up, verification and implementation of screening for SMA

Parameter	Units	Unit cost[†]	95% CI	Distribution	Source
Laboratory set up and verification					
ICT updates	NA	€40,000	€32,402 to 48,387	Gamma	NNBSP[86]
Thermal cycler	2	€15,000	€12,604 to €17,601	Gamma	
Centrifuge	2	€7,600	€6,117 to €9,135	Gamma	
Other laboratory equipment and supplies (for example, pipettes)	NA	€12,000	€9,720 to €14,516	Gamma	
Test kits for verification	10	€7,000	€5,670 to €8,468	Gamma	
Implementation					
SMA screening test[‡]	≈60,000 per annum	€2.00	€1.62 to €2.42	Gamma	NNBSP[86]

Key: CI – confidence interval; ICT – information and communications technology; NA – not applicable; NNBSP – National Newborn Bloodspot Screening Programme; SMA – spinal muscular atrophy.

[†] Uncertainty in cost parameters was represented by 20% variation in the mean value.

[‡] The cost presented represents the incremental cost associated with the addition of SMA to the testing panel, assuming a multiplex testing assay is used to simultaneously screen for SMA and SCID. The total test kit cost to screen for SMA and SCID concurrently is estimated at approximately €6 to €7 per test.

Table 7.3 Cost of additional staff requirements

Parameter	Units	Unit cost†	Distribution	Source
Clinical staff				
Senior clinical psychologist	1	€137,033	Gamma	HSE salary scales[241]

Key: HSE - Health Service Executive.

† 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. Uncertainty in cost parameters was represented by 20% variation in the mean value.

Table 7.4 Healthcare utilisation costs associated with treatment administration and outcome monitoring

Parameter	Unit(s) per patient	Unit cost	95% CI[†]	Distribution	Source
Treatment with OA					
Inpatient admission in year 1 of treatment	1 (LOS 10 days)	€17,863[‡]	€14,470 to €21,608	Gamma	ABF 2023 Admitted Patient Price List[(240)]
Outpatient appointment for monitoring in year 1	8 (range 4 to 12) in year 1	€195	€158 to €236	Gamma	HPO[(242)]
Outpatient appointment for long-term follow-up	2.5 (range 2 to 3) per annum			Gamma	
Treatment with nusinersen					
Daycase admission in year 1 of treatment	4 to 6 in year 1	€1,295[§]	€1,049 to €1,567	Gamma	ABF 2023 Admitted Patient Price List[(240)]
Daycase admission for maintenance dosing	3 per annum			Gamma	ABF 2023 Admitted Patient Price List[(240)]
Treatment with risdiplam					
Outpatient appointment for monitoring in year 1	8 (range 4 to 12) in year 1	€195	€158 to €236	Gamma	HPO[(242)]
Outpatient appointment for long-term follow-up	2.5 (range 2 to 3) per annum			Gamma	

Key: ABF – Activity Based Funding; HPO – healthcare pricing office; LOS – length of stay; OA – onasemnogene abeparvovec.

[†] Uncertainty was represented by 20% variation in the mean value.

[‡] 'Procedures for cerebral palsy, muscular dystrophy and neuropathy, intermediate complexity'.

[§] 'Infusion for musculoskeletal disorders, same day'.

All medication costs were adjusted in line with guidance from the National Centre for Pharmacoeconomics.[171] Adjustments included wholesale mark-up and the rebate mandated by the framework agreement on the supply and pricing of medicines. A pharmacy dispensing fee was applied to drugs dispensed in the community setting (that is, risdiplam). Non-oral medicines (that is, OA and nusinersen) were subject to VAT at 23%.[243] The total estimated drug cost to the HSE at the publicly available list price is presented in Table 7.5.

As outlined in chapter 5, patients treated with nusinersen receive four loading doses following by maintenance dosing every four months (see chapter 5, Table 5.1).[29] On average, patients were estimated to receive four to six doses of nusinersen in the first calendar year of the BIA due to differences in the timing of diagnosis and subsequent treatment initiation.

In line with the summary of product characteristics, the recommended once daily dose of risdiplam was adjusted for weight and age.[30] At the time of the analysis (August 2023), the minimum licenced age for initiation of risdiplam was two months. While the summary of product characteristics now permits initiation from birth, this change will not alter base case results given no patients in the screening arm were modelled as starting treatment at this age and the minimum age for reimbursement remains at two months. The median weight (50th centile) for children aged zero to six years was estimated using UK-WHO growth charts which have been adopted for use in Ireland.[244, 245] The recommended daily dose ranges from 0.20 mg/kg (2 months to < 2 years of age) up to 5 mg (≥ 2 years of age (≥ 20 kg)).[30] Children reach 20 kg by approximately six years of age, on average, based on UK-WHO growth charts.[244, 245] Therefore, average daily doses were assumed to be constant and to remain at the maximum licensed dose of 5 mg after six years of age.

The evidence base at the point of regulatory approval considers OA, nusinersen and risdiplam as standalone treatments.[29-31] Concomitant or sequential treatment with two or more of these agents has not typically been observed in clinical practice in the Irish setting.[26] Therefore, for the purposes of this BIA, treatments were assumed to be mutually exclusive.

Table 7.5 Cost of disease-modifying therapies

Parameter	Dosage information	Annual cost		Source
		Excl. VAT	Incl. VAT†	
Onasemnogene abeparvovec	One-off treatment in year of diagnosis	€1,759,447	€2,201,713	CPU[175] (Publicly available price‡)
Nusinersen	6 doses in the year of diagnosis (4 loading doses, and 2 maintenance doses)	€407,397	€509,802	CPU[175] (Publicly available price‡)
	Maintenance doses (3 doses per annum)	€203,698	€254,901	
Risdiplam§	Daily; Age 2 to 12 months	€80,098	€80,098	MMP[173] (Publicly available price‡)
	Daily; Age 1 to 2 years	€106,633	€106,633	
	Daily; Age 2 to 3 years	€163,144	€163,144	
	Daily; Age 3 to 4 years	€190,054	€190,054	
	Daily; Age 4 to 5 years	€217,903	€217,903	
	Daily; Age 5 to 6 years	€246,065	€246,065	
	Daily; Age ≥6 years	€251,072	€251,072	

Key: CPU – Corporate Pharmaceuticals unit in the Health Service Executive; MMP – Medicines Management Programme; VAT – value added tax.
† A zero VAT rate applies to oral medicines.[246]
‡ Cost estimates are based on the published list price. The costs presented include the ingredient cost, dispensing fees and tax adjustments (that is, VAT and Framework Agreement Rebate), where applicable. Actual drug costs may be lower than presented due to the potential for confidential pricing agreements between pharmaceutical companies and the HSE.
§ The recommended once daily dose of risdiplam varies according to weight and age. Estimated costs were based on the mean weight for each age group according to UK-WHO growth charts.[244, 245]

Sensitivity and scenario analysis

Parameter uncertainty was investigated using a Monte Carlo approach with 5,000 simulations. Each model parameter was predefined by a statistical distribution which represented uncertainty in the mean parameter value. Parameter values were drawn at random from their probability distribution.

The range of plausible values for scheduled care associated with treatment administration and outcome monitoring was based on the treatment pathway, outlined in chapter 2. Uncertainty associated with timing of clinical presentation in the current care arm, and amongst cases with four to six *SMN2* copies in the screening cohort was accounted for by staggering the timing of treatment initiation over time (see Appendix Chapter 7, Table A7.1). Where no plausible estimates of uncertainty were available, uncertainty in non-drug cost parameters was represented by 20% variation in the mean value. Drug costs were excluded from the PSA. Given that the publicly available price represents an upper bound, scenario analysis was considered to be a more appropriate method to capture the uncertainty.

In each scenario analysis, model assumptions were changed, or a base case parameter was replaced with an alternative estimate. The estimated equipment requirements associated with the establishment of diagnostic testing at an alternative site in Ireland are presented in Table 7.6. Additional parameters and assumptions that were subject to considerable uncertainty, and/or were expected to have a considerable impact on the budget impact were also investigated in scenario analysis. In particular, due to the potential for confidential pricing agreements between pharmaceutical companies and the HSE as part of patient access schemes, the true cost of disease-modifying treatments drugs may be lower than presented. Potential price reductions relative to the assumed upper bound were investigated in scenario analysis. Also a scenario examining immediate treatment for those with four *SMN2* copies in the screening arm was modelled. At the time of the analysis (August 2023), the minimum age for initiation of risdiplam under the EMA license was two months. While the summary of product characteristics now permits initiation from birth, the published minimum age for reimbursement remains at two months (as of September 2023). Scenario analyses were based on the deterministic value.

Table 7.6 Inputs used in scenario analyses

Scenario	Parameter(s)	Units	Estimate	Source
Diagnostic testing at an alternative site	Cost of a thermal cycler	1	€15,000	NNBSP[86]
	Cost of capillary electrophoresis instrument	1	€40,000	
	Cost of MLPA test kit	1	€2000	
	Physical space for sample preparation and analysis†	NA	NA†	
Decrease the incidence of SMA	Incidence of screen-detected SMA	NA	6.3 per 100,000	Chapter 3
Increase the incidence of SMA	Incidence of screen-detected SMA	NA	25.5 per 100,000	Chapter 3
Vary drug costs	Cost of nusinersen	NA	€42,484 (50% reduction)	Assumption
	Cost of OA	NA	€1,100,857 (50% reduction)	
	Cost of risdiplam at 2 to 12 months*	NA	€3,337 (50% reduction)	
	Cost of risdiplam at 1 to 2 years*	NA	€4,433 (50% reduction)	
	Cost of risdiplam at 2 to 3 years*	NA	€6,798 (50% reduction)	
	Cost of risdiplam at 3 to 4 years*	NA	€7,919 (50% reduction)	
	Cost of risdiplam at 4 to 5 years*	NA	€9,079 (50% reduction)	
	Cost of risdiplam at 5 to 6 years*	NA	€10,253 (50% reduction)	
	Cost of risdiplam at 6 to 9 years*	NA	€10,461 (50% reduction)	

Scenario	Parameter(s)	Units	Estimate	Source
Vary proportions prescribed nusinersen versus risdiplam	Proportion of patients treated with nusinersen	NA	100%	Assumption
	Proportion of patients treated with risdiplam	NA	100%	Assumption

Key: MPLA - Multiplex-ligation dependent probe amplification; NA – not applicable; NNBSP – National Newborn Bloodspot Screening Programme; OA – onasemnogene abeparvovec; VAT – value added tax.

† It was assumed that additional space would be allocated in the New Children's Hospital, if necessary, without requirements for modification of existing or construction of additional infrastructure.

‡ Applies to patients with types II and III SMA in the current care arm, and patients with four to six copies of *SMN2* managed with nusinersen or risdiplam in the screening cohort only.

* The costs of risdiplam across all age groups were reduced across a single scenario.

Quality assurance

The BIA was developed in accordance with national HTA guidelines,[235] 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.

7.3.2 Results

The incremental budget impact associated with the potential addition of screening for SMA to the NNBSP is presented for three main cost categories:

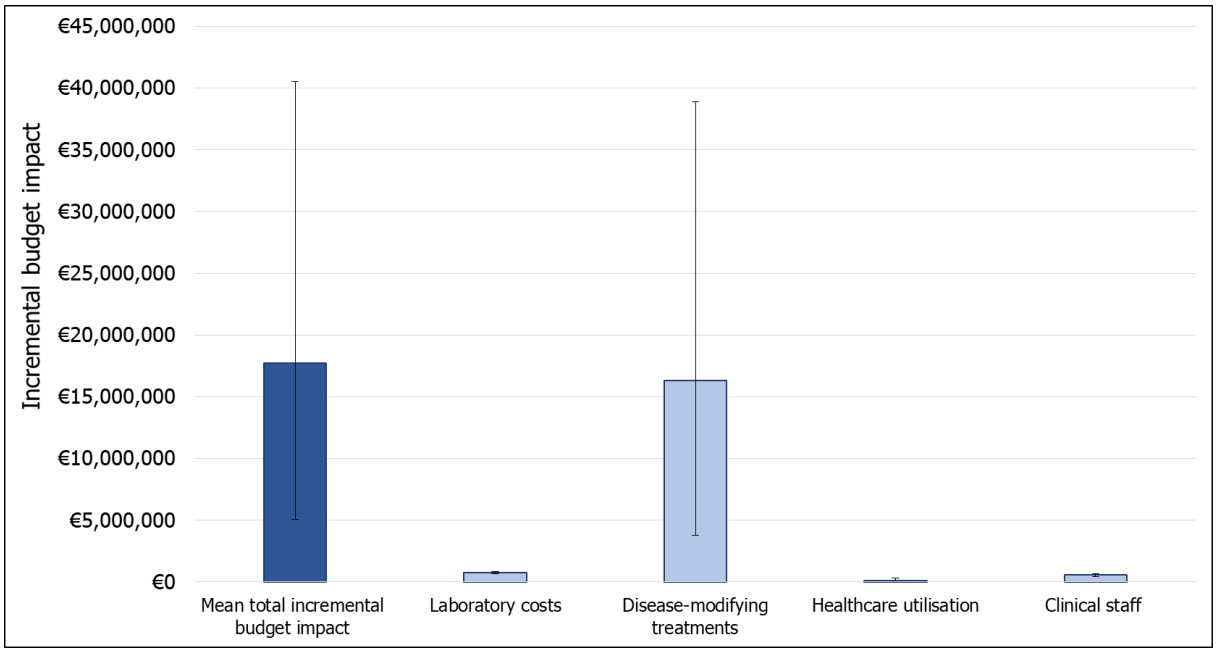
- verification and implementation of screening (for example, laboratory equipment, consumables, recruitment of staff)
- pharmacological treatment (for example, OA, nusinersen, risdiplam)
- healthcare utilisation (for example, daycase, inpatient and outpatient appointments).

Base case analysis

Over a five-year time horizon, the incremental budget impact associated with the addition of screening for SMA to the NNBSP (that is, the budget impact over and above current expenditure in the absence of screening), was estimated at €17.7 million (95% confidence interval (CI): €5.1 to €40.5) (Figure 7.2). The majority of expenditure over this period (> 90%) was related to drug costs (€16.3 million, 95% CI: €3.8 to €38.9). The costs of scheduled healthcare utilisation (€0.1 million, 95% CI: €0.02 to €0.3) and clinical staff (€0.5 million, 95% CI: €0.4 to €0.7) comprised a small proportion of the total incremental budget impact (< 5%). Total laboratory costs, comprising equipment and consumables, were estimated at €0.7 million (95% CI: €0.6 to €0.8).

The five-year time horizon comprises one year of laboratory verification and four years of post-implementation screening. Over this time horizon the total budget impact of €17.7 million is largely accounted for by the earlier diagnosis and associated consequences for the treatment of SMA for approximately 25 patients. This is equivalent to an incremental budget impact of approximately €0.7 million per patient identified and treated earlier than they would be in the absence of screening, specifically considering the modelled costs associated with the first five years of the programme. Implications of considering a longer time horizon and the exploration of uncertainty are presented in the scenario analysis below.

Figure 7.2 Itemised five-year incremental budget impact



Errors bars represent the 95% CI for the mean. 'Disease-modifying treatments' includes onasemnogene abeparvovec, nusinersen and risdiplam.

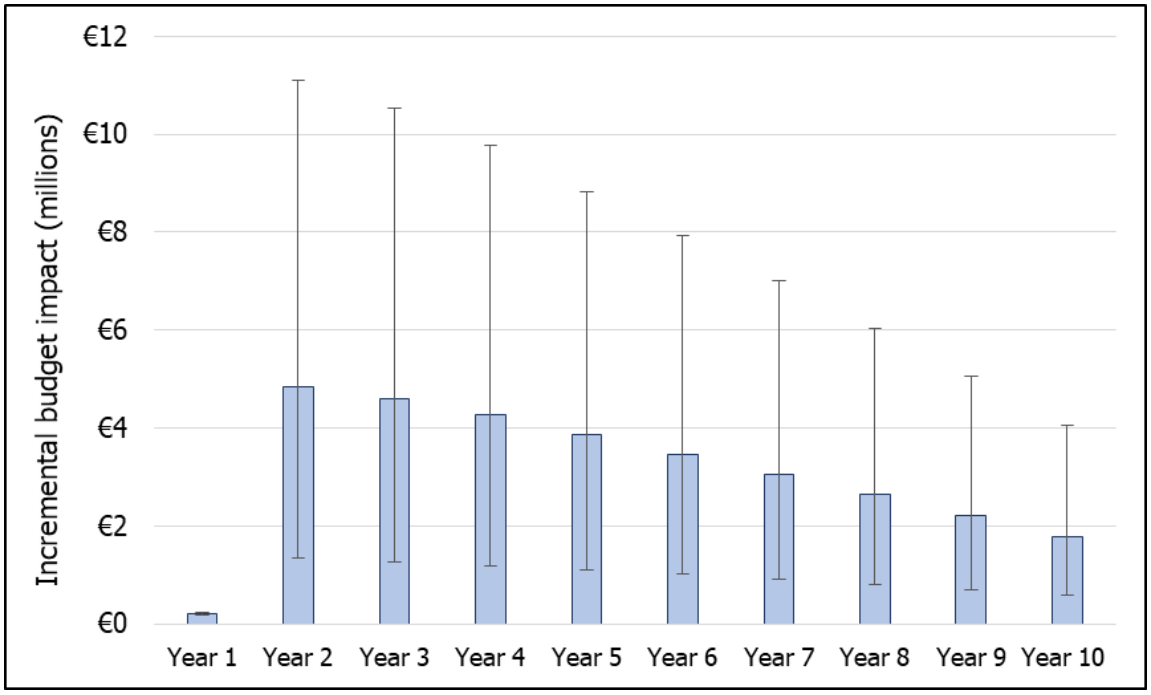
Scenario analysis

Data and structural uncertainties were investigated in scenario analyses to estimate the impact of changes in key input parameters or assumptions on the incremental budget impact. Results of key scenarios are described below.

Ten-year time horizon

Due to differences in the distribution of prices over time between available disease-modifying treatments (for example, one-off treatment versus ongoing maintenance costs), a ten-year time horizon was considered in scenario analysis to capture potential changes in the direction and magnitude of the budget impact over time. Over a ten-year time horizon, the incremental budget impact was estimated to be €30.9 million (95% CI: €9.4 to €73.0). A trend towards a decrease in the annual incremental budget impact over time was observed (Figure 7.3).

Figure 7.3 Annual incremental budget impact over a ten-year time horizon



Year 1 includes laboratory set up and verification of the screening test. No differences in the cost of treatment and monitoring between the cohorts were assumed in year 1. Implementation of screening was assumed to commence in year 2.

Incidence of SMA

The incidence of SMA in the Irish context is subject to considerable uncertainty due to the rarity of the disease and the potential for a long prediagnostic period for patients with milder types of SMA. In scenario analysis, the incidence of SMA was varied using the upper and lower bound from the international data (chapter 3). Increasing the estimated incidence of SMA to the upper bound (that is, 1 in 4,394 live births) of the plausible range resulted in an increase in the five-year incremental budget impact of €15.8 million (95% increase) relative to the base case of €17.7 million. Setting the incidence of SMA to the lower bound (that is, 1 in 24,423 live births) resulted in a decrease of €9.7 million (58%) in the incremental budget impact when compared with the base case. The relative change in the incremental budget impact as a result of setting the incidence to the upper or lower bound was broadly consistent over a ten-year time horizon (data not shown).

Treatment strategy

In the base case analysis, it was assumed that patients with four or more copies of *SMN2* identified through screening would be managed with watchful waiting. The potential for all patients with four *SMN2* copies to be treated from the point of diagnosis was investigated in scenario analysis. Presymptomatic treatment of all patients with four *SMN2* copies was estimated to be associated with an increase of €0.9 million (6%) in the incremental budget impact (Figure 7.4). The observed difference was modest owing to the estimated small proportion of cases identified

through screening that would carry four copies of *SMN2,* based on the available epidemiological data (Figure 7.4). Over a ten-year time horizon, treatment of all patients with four *SMN2* copies from the point of diagnosis resulted in an increase of €3.4 million (12%) in the incremental budget impact relative to the baseline estimate of €30.9 million (data not shown). Of note, a considerable proportion of cases with four *SMN2* copies would be expected to present with less progressive disease types (for example, type III SMA) in the current care arm. Therefore, the additional cost associated with treating patients with four *SMN2* copies from the point of diagnosis in the screening cohort becomes more pronounced over longer-term time horizons.

In the base case analysis, it was assumed that nusinersen and risdiplam would be prescribed in equal proportions for patients in the current care arm with types II and III SMA, and for patients with four to six copies of *SMN2* presenting with symptoms from six months of age in the screening cohort. Over shorter-term time horizons, differences in the cost of treatment with nusinersen and risdiplam are driven by the requirements for four maintenance doses in the first year of treatment for patients treated with nusinersen, and the use of weight/age-based dosing for children under six years treated with risdiplam (see Table 7.5).As a result, the absolute cost of treating a child with risdiplam is lower relative to nusinersen, based on published list prices over the first six years. After the age of six, the annual cost of nusinersen and risdiplam is almost equivalent at the list price.

In scenario analysis, the proportion of patients with types II and III SMA in the current care arm, and with four to six copies of *SMN2* managed with (i) nusinersen versus (ii) risdiplam in the screening cohort was set to 1.0 in turn (that is, in the first scenario, 100% of patients receive nusinersen, while in the second scenario, 100% of patients receive risdiplam). Under the assumption that 100% of patients (excluding patients with type I SMA and patients with less than three *SMN2* copy numbers) would be treated with nusinersen, the incremental budget impact over a five-year time horizon decreased by €0.9 million (6%) relative to baseline (€17.7 million). Over a ten-year time horizon, the decrease relative to baseline was €3.1 million (11%). Given the inverse relationship between the proportion of patients being treated with either drug, the change in the incremental budget impact for the assumption that 100% of these patients would receive risdiplam, was the same as for the 100% nusinersen scenario, but in the opposite direction (that is, an increase of €0.9 million over a five-year time horizon and an increase of €3.1 million over a 10-year time horizon). The relative increase in the incremental budget impact in the context of risdiplam comprising 100% of the prescribed treatments in the sub-cohort of patients with types II and III SMA, and those with four to six copies of *SMN2*, was attributable to the consequent lower cost of treatment in the current care arm. As a result, the absolute difference in the cost of treatment between the current care and screen cohorts was greater (Figure 7.4). Of note, due to the open-cohort structure

of the model, the impact of the decreasing difference in annual cost between risdiplam and nusinersen in older patients (more than six years of age) is not apparent.

Drug pricing

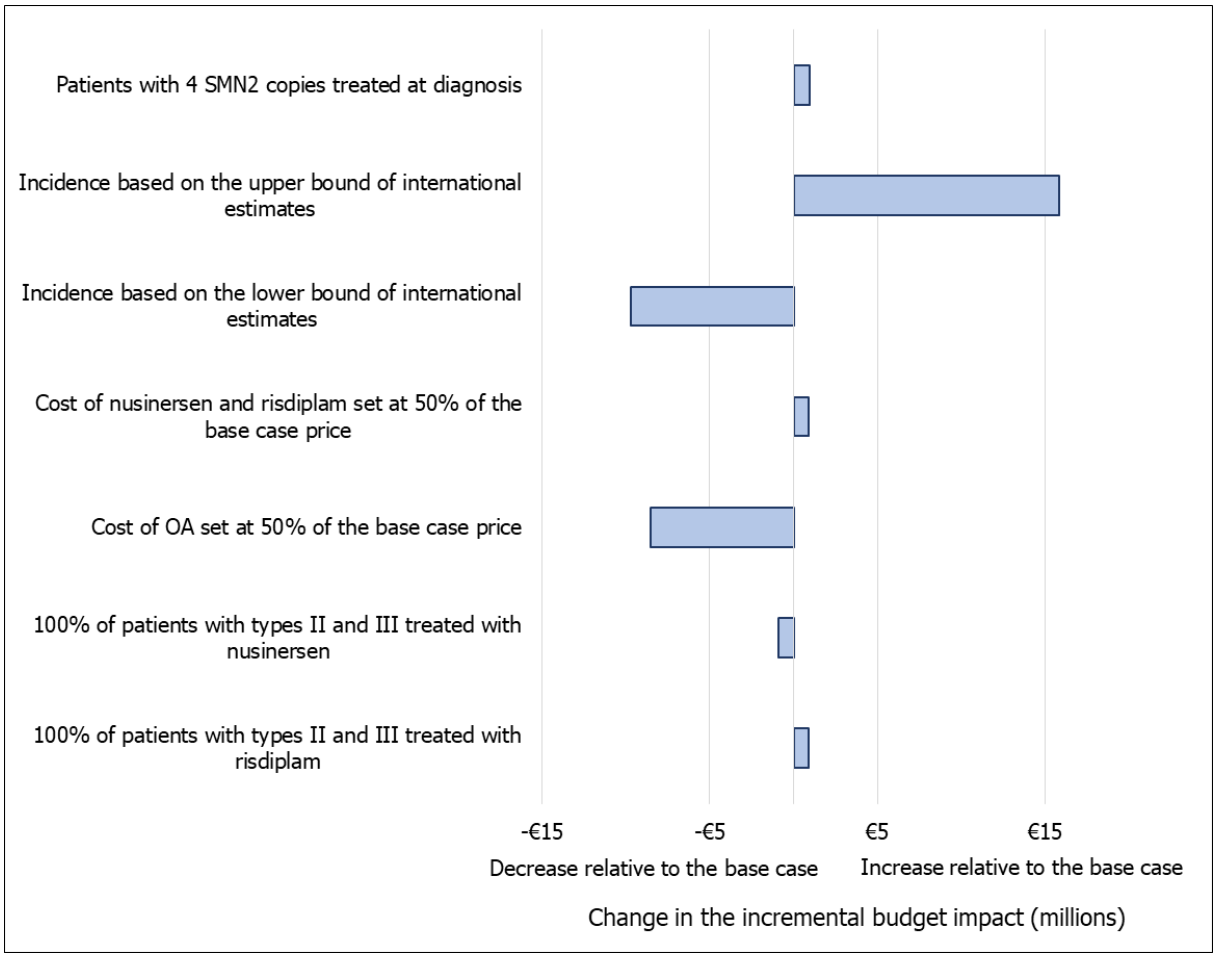
It is likely that the addition of screening for SMA to the NBBSP would be associated with changes in treatment assignment due to the absence of complete correlation between genotype and phenotype. In the base case analysis, it was estimated that screening would be associated with an increase in the proportion of patients treated with OA relative to current care, and a corresponding reduction in the number of patients managed with other disease-modifying treatments (that is, nusinersen and risdiplam). Due to these assumed differences in treatment assignment between the standard care and screening cohorts, the absolute difference in the incremental budget impact between these cohorts is greatest when the difference between the cost of OA and other disease-modifying treatments (that is, nusinersen and risdiplam) is greatest.

In scenario analysis, a 50% reduction in the cost of OA relative to the base case price was estimated to result in a decrease of €8.5 million (51%) in the five-year incremental budget impact (Figure 7.4). Over a ten-year time horizon, a 50% reduction in the base case price of OA resulted in a decrease of €19.1 million (67%) in the incremental budget impact, owing to a reduction in the cost of treatment in the screened cohort. Conversely, a 50% reduction in both the cost of nusinersen and risdiplam resulted in an increase of €0.9 million (6%) in the incremental budget impact over a five-year time horizon. Importantly, over a ten-year time horizon, a 50% reduction in the cost of nusinersen and risdiplam resulted in an increase of €6.3 million (22%) in the incremental budget impact (data not shown). The observed relative increase in the incremental budget impact associated with a reduction in the assumed cost of risdiplam and nusinersen was attributable to the consequent lower cost of treatment in the standard care cohort. As a result, the time taken to offset the cost of treating the majority of patients in the screening cohort with OA (85%) increased relative to the standard care cohort.

Location of confirmatory testing

Based on consultation with the NNBSP, it is anticipated that diagnostic testing would take place in the Molecular Genetics Laboratory at CHI Crumlin, consistent with current practice for patients identified based on clinical suspicion or family history. In the event that the number of positive screens exceeds availability capacity for diagnostic testing at the Molecular Genetics Laboratory at CHI Crumlin, it is estimated that establishing diagnostic testing capacity at the NNBSL or an alternative site would cost approximately €57,000 in addition to estimates presented in the base case analysis (data not shown).

Figure 7.4 Results of scenario analyses relative to the base case over a five year time horizon



Key: OA - onasemnogene abeparvovec; SMA – spinal muscular atrophy; *SMN2 – spinal muscular neuron 2*.

Alternative estimates for key input parameters were tested in scenario analysis. Results are presented as the change relative to the total five-year incremental budget impact.

7.4 Discussion

This chapter presented the additional resources and associated costs related to the potential addition of screening for SMA to the NNBSP in Ireland. In the context of screening, management of SMA is complicated by the potential for variability in genotype-phenotype relationships. Key organisational considerations arising from this therefore include the clinical care pathway for patients estimated to be at lower risk of disease progression based on known prognostic factors. From a laboratory perspective, the greatest challenges associated with the addition of screening for SMA to the NNBSP would be infrastructural constraints at the existing site of the NNBSL, which would likely impede implementation of screening until the laboratory is operational at the new children's hospital, and uncertainty regarding laboratory capacity at CHI Crumlin to undertake second-tier testing.

The overall incremental budget impact associated with screening for SMA was estimated at €17.7 million (95% CI: €5.1 to €40.5) over a five-year time horizon. The results were subject to considerable uncertainty due to limited evidence underpinning key input parameters. Varying the incidence of SMA based on alternative estimates from the international literature had a significant impact on the estimated incremental budget impact. The cost of disease-modifying treatments, in particular OA, also had a considerable influence on the modelled output.

Organisational considerations

A number of organisational implications that are common to any new addition to the NNBSP have been covered in detail in a previous HIQA HTA of the addition of screening for SCID to the NNBSP, and hence were not repeated in the present HTA.[10] Some considerations specific to the introduction of newborn bloodspot screening for SMA were identified.

From a laboratory perspective, the main challenges associated with the potential implementation of screening for SMA relate to infrastructural constraints at the existing site of the NNBSL, and potential staffing shortages. Due to a lack of physical space, implementation of screening at the NNBSL is unlikely to be possible until the new laboratory at the new children's hospital is operational. If a decision is made to implement screening for SMA, should there be further delays associated with the opening of the new children's hospital it may be necessary to undertake verification of the testing method at a satellite site to facilitate timely implementation. A further potential challenge to implementation relates to the ongoing national shortage of medical laboratory scientists across the public service.[247] In the event that a positive recommendation to implement screening for SMA is made, failure to fill these positions may put pressure on existing activities at the NNBSL, including the

potential suboptimal performance outcomes including increased test turnaround times.

In terms of confirmatory testing capacity, it is not anticipated that additional staff would be required should second-tier testing be implemented in the Molecular Genetics Laboratory at CHI Crumlin. However, should the observed number of cases and false positives exceed the expected number based on the international literature, additional staffing at CHI Crumlin or establishment of confirmatory testing at the NNBSL may be required. For the purposes of the budget impact analysis, an exhaustive list of all potential options was not investigated in scenario analyses. The optimal approach to confirmatory testing would likely depend on the outcome of verification processes, and would require consideration of potential barriers or facilitators to implementation at each site at the point of service planning. It is important to note that from a diagnostic testing perspective, the availability of screening for SMA would not remove the need for diagnostic testing of patients presenting clinically with neuromuscular symptoms of unknown origin given that screening for SMA cannot identify patients with compound heterozygous variants (up to 5% of cases). Additionally, in the event that screening for SMA is introduced, cases born prior to its introduction will continue to present clinically with symptoms in the long-term due to the long prediagnostic period for milder SMA types.

In terms of clinical pathways in the context of the introduction of screening for SMA, a number of considerations were identified concerning the referral pathway and treatment pathway. The decision over whether or not to introduce second-tier testing will influence the referral pathway. Regardless of the approach taken, careful multidisciplinary consideration of the referral pathway will be required to ensure access to care is efficient and timely. In terms of treatment pathways, if newborn bloodspot screening for SMA is introduced, decision-making regarding treatment will be made on the basis of *SMN2* copy number, and not SMA type as has been the case historically. The treatment pathway will likely change, with some cases likely receiving an alternative therapy than they would have received if they had presented symptomatically at a later point.

Additionally, as screening for SMA would identify cases in infancy rather than cases presenting clinically at some point, there are implications for clinical capacity given that cases, whether treated with pharmacological agents or not, would require access to care and monitoring from an earlier point than in the absence of screening. Consideration would be required to ensure that demand is met. Those identified with SMA through screening who are placed on a watchful waiting strategy would require ongoing monitoring in the outpatient setting. However, such individuals, that is, those with higher *SMN2* copy numbers, represent a small proportion of cases with SMA, based on the available epidemiological data and outcomes of existing screening programmes. In the longer-term, as the number of

patients requiring long-term follow-up increases, additional multidisciplinary capacity may be required to ensure there is sufficient capacity to meet demand for follow-up care.

Budget impact analysis

The incremental budget impact associated with the potential addition of screening for SMA to the NNBSP was presented for the cost categories of (i) laboratory costs; (ii) pharmacological treatment; and (iii) scheduled healthcare utilisation. Results of the budget impact analysis found that the majority of costs were accounted for by pharmacological treatment (approximately 90%), with laboratory costs and healthcare utilisation costs each accounting for approximately 5% of the budget impact.

SMA is associated with significant morbidity and mortality. While studies assessing healthcare utilisation among patients with SMA are limited, the available evidence indicates high resource use and financial costs. Studies reporting on healthcare utilisation were, however, typically undertaken prior to the availability of disease-modifying treatments, did not have a comparator group, or were not considered applicable to the Irish context due to differences in healthcare system characteristics.[115-118, 154, 248-250] Only one study was identified comparing early diagnosis with standard care in terms of healthcare utilisation.[154] In this study, total direct care costs were lower for patients identified early (due to sibling diagnosis or through screening) than treated symptomatic patients, which highlights the potential for screening to result in reduced healthcare utilisation and expenditure related to management of disease signs and symptoms.[154] However, costs were reported at an aggregate level only, without information on the underlying resource use, precluding its consideration in this BIA. Due to the limitations in the evidence base, this BIA only considered scheduled care costs related to diagnosis, treatment and monitoring. It is plausible, however, that improved clinical outcomes in the screened cohort may be associated with a reduction in requirements for inpatient hospitalisation, emergency department attendance, allied health professional visits and home care resulting in potential cost offsets.

Furthermore, evidence from a retrospective cohort study in the United States demonstrated that the introduction of nusinersen resulted in a shift in the setting of care for patients with type I SMA.[118] Costs for inpatient and outpatient care accounted for 63% and 11% of total healthcare utilisation costs, respectively, in the overall type I SMA cohort.[118] In the sub-cohort treated with nusinersen, inpatient and outpatient care accounted for 36% and 27% of healthcare utilisation, respectively. However, it is unclear how total care, inclusive of drug costs, for patients with SMA type I treated with nusinersen compared with that for the overall cohort. Excluding nusinersen-related costs, total mean healthcare costs per patient

per year were lower among patients with SMA type I treated with nusinersen, relative to healthcare costs for the overall cohort with SMA type I. It is plausible that earlier identification through screening would be associated with a further shift in the setting of care, from inpatient to outpatient, relative to patients treated following symptom onset, and a consequent reduction in the cost of healthcare utilisation.

With regard to the costs of verification and implementation of screening, during consultation with key stakeholders it was noted that concurrent, rather than sequential, addition of SMA and SCID to the NNBSP would be associated with operational efficiencies. However, given that screening for SCID is not yet in place, and in the context of other organisational uncertainties including the upcoming move to the new children's hospital, estimation of the incremental equipment requirements needed to facilitate the addition of SMA to the NNBSP is challenging. The cost of such equipment and consumables would be subject to the outcome of a formal tendering process prior to procurement;[239] therefore, the costs of these supplies cannot be estimated with certainty. In particular, for the purposes of this HTA, it was assumed that all equipment would be purchased, rather than leased, due to challenges associated with estimating the cost of leasing agreements prior to a formal tendering process. Equipment leasing may have advantages including lower upfront costs, ease of upgrade to newer products, and repair or maintenance costs are typically included in the leasing agreement. However, leasing is typically more expensive in the long term compared with capital investment. The distribution of costs over time would vary between capital investment and leasing. The estimates provided were based on the knowledge of key stakeholders at the time of analysis. However, if a decision were made to add SMA to the NNBSP, amendments to the proposed requirements for laboratory equipment and consumables may need to be made at the point of service planning. Furthermore, in practice, testing outcomes would be dependent on context-specific testing protocols developed during assay verification, as well as the epidemiology of the screened population. Given uncertainty regarding testing outcomes and the local epidemiology of disease, it is challenging to determine if there is sufficient capacity to conduct confirmatory testing, alongside existing activities, within existing resources at the Molecular Genetics Laboratory at CHI Crumlin. As noted previously, the potential requirement to establish confirmatory testing at the NNBSL, or potential recruitment of additional staff at the Molecular Genetics Laboratory at CHI Crumlin, would require additional investment.

The payer perspective was considered most important in the context of this BIA, where only costs and resources relevant to the HSE were included in the analysis. Consideration of a broader societal perspective was not possible due to the lack of data comparing current practice with screening in terms of indirect costs (for example, productivity losses for individuals and their carers, and home

modifications). Although the evidence base is limited, the availability of disease-modifying treatments has been reported to reduce caregiver burden as measured with quality-of-instruments.[251] A cross-sectional survey of patients with SMA in which 78% of participants were managed with disease-modifying treatments reported that among parents of children with type I SMA, there was a tendency for only one parent to be employed when compared with parents of children with other SMA types.[252] The extent to which screening can circumvent loss of motor skills in those with more progressive disease types is unclear, given that a proportion of patients will be symptomatic at the time of treatment initiation even if screening is available. Nevertheless, it is likely that earlier intervention would be associated with improved motor outcomes, which may translate into broader societal benefits including improved social functioning and labour market participation.

As noted, the costs of providing disease-modifying treatments, in particular OA, had a considerable influence on the modelled budget impact. In scenario analysis, varying the incidence of SMA was demonstrated to have a significant influence on the estimated incremental budget impact. It is important to note, however, that it is not just the absolute number of cases that drives the incremental budget impact, but rather the assumed distribution of *SMN2* copy numbers within the screened cohort, which gives rise to differences in the treatment pathway between the standard care and screening cohorts. In the context of screening, it was assumed that approximately 85% of cases would carry three of fewer copies of *SMN2* and be eligible for treatment with OA. Under current practice, based on SMA type, it is estimated that approximately 55% of patients would be treated with OA.

There is considerable uncertainty regarding the risk-benefit balance of presymptomatic treatment in patients with four or more *SMN2* copies. This is because the majority of clinical trials undertaken in presymptomatic patients were limited to patients with up to three copies of *SMN2* (chapter 5). In the base case analysis it was assumed that only patients with three or fewer *SMN2* copies would be treated with OA at the point of diagnosis. However, treatment of patients with four *SMN2* copies with nusinersen or risdiplam is within the scope of their licenced indications, as outlined by the EMA. In scenario analysis, the potential for all patients with four *SMN2* copies identified through screening to be treated from the point of diagnosis was investigated. Presymptomatic treatment of all patients with four *SMN2* copies was estimated to be associated with a modest increase in the incremental budget impact, as based on the available epidemiological data, cases with four copies of *SMN2* are estimated to comprise a small proportion of overall cases. As discussed in chapter 3, the applicability of available epidemiological estimates to the screening context is uncertain, as these estimates only include the subset of patients who presented clinically in the absence of screening. It is important to consider that identification of symptom onset may occur earlier in the context of a watchful

waiting strategy. In this regard, the incremental budget impact presented here may be underestimated. However, the absolute impact is likely to be marginal, given that the majority of patients in the screened cohort were modelled to be treated with OA, under the assumption of one-off treatment.

The choice of disease-modifying treatment has considerable implications for the cost-effectiveness and affordability of screening and earlier treatment initiation. As described in chapter 6, treatment of patients with OA, rather than nusinersen, was generally considered more cost effective over longer-term time horizons, subject to the assumptions modelled. When considered as alternative treatment strategies, based on the published list price, it is estimated that the total cost of pharmacological treatment per patient is equivalent between a patient managed with OA and a patient managed with nusinersen after approximately eight years, and after 11 years for a patient managed with risdiplam. This is due to the assumed requirement for ongoing maintenance dosing among patients treated with nusinersen or risdiplam, relative to assumed one-off treatment with OA. Importantly, however, in the present BIA, an increase in the proportion of patients treated with OA relative to current care was associated with an increase in in the incremental budget impact in the short-term owing to the high upfront cost of OA. The time taken to offset the initial upfront investment associated with an increase in the proportion of patients managed with OA in the context of screening is highly dependent on the drug prices agreed between the HSE and pharmaceutical companies as part of patient access schemes.

In this analysis, each of the available disease-modifying treatments were considered standalone treatments, consistent with the evidence base at the point of regulatory approval.[29-31] However, sequential use of at least two of these treatments is not outside the scope of their licences or reimbursement protocols, and has been observed in the clinical setting in other European countries, in the context of suboptimal treatment outcomes with OA.[253-256] As noted in a report published by the Healthcare Institute of the Netherlands, there is no published evidence that a combination of two or more disease-modifying treatments is superior to any single treatment alone.[254] The results of a phase 4 clinical trial investigating subsequent nusinersen treatment among patients previously treated with OA that is currently underway will be important to inform clinical practice regarding the safety and efficacy of concomitant treatment (estimated study completion date: September 2024).[257] The use of sequential therapy, if demonstrated to be associated with improved clinical outcomes, would result in increased spending on disease-modifying treatments, with or without the introduction of screening. The potential for sequential treatments was not investigated in this analysis given the availability of short- to medium-term clinical effectiveness data for available disease modifying treatments. Over longer-term time horizons typically used in cost utility analyses,

potential requirements for concomitant treatment should be considered, given the lack of long-term clinical effectiveness data.

7.4.1 Limitations

Consistent with national guidelines for the conduct of budget impact analysis of health technologies in Ireland, this analysis estimates costs over a short-term time horizon consistent with current national budgeting processes and periods. Forecasting costs over longer-term time horizons are impractical due to the requirement for considerable assumptions. An important limitation of this approach is that due to variation in age at clinical presentation across the disease spectrum, some cases with type III SMA and all cases with type IV SMA will not present within the time horizon of this analysis. Based on the available epidemiological data, these cases represent approximately 10% of all cases. Therefore, it is likely that disease management costs for the majority of cases have been accounted for in the present analysis. As noted previously, a short-term budget impact cannot capture the potential for a reduced total spend per patient in the longer-term associated with differences in treatment assignment occurring in the screened cohort, relative to current practice.

A high level of uncertainty is inherent to research related to rare diseases and to the estimated cost of policy proposals prepared for future years. Probabilistic and scenario analysis demonstrated a substantial degree of uncertainty around the point estimate, largely attributable the potential for considerable variation related to epidemiological inputs, the cost of disease-modifying treatments, and knowledge gaps related to reimbursement criteria for available disease-modifying treatments. Conclusions about the affordability of screening for SMA should be reached by judgment of the modelled outputs in light of the considerable uncertainty.

7.4.2 Conclusions

In the context of screening, treatment of SMA is complicated by the potential for variability in genotype-phenotype relationships. Therefore, the addition of screening for SMA to the NNBSP would result in changes in treatment pathways for patients identified through screening relative to current practice. This would have resource and budget implications for the HSE.

Over short-term time horizons, screening for SMA and subsequent treatment would result in very high upfront costs. The requirement for additional investment may diminish over time, however this is highly dependent on the cost of disease-modifying treatments and the epidemiology of SMA types in the Irish context.

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

Key points

- This chapter outlines the potential ethical and social considerations associated with the addition of spinal muscular atrophy (SMA) to the National Newborn Bloodspot Screening Programme (NNBSP) in Ireland. Four main topic areas are considered: benefit – harm balance, autonomy, justice and equity, and ethical consequences of the HTA. Some ethical and social considerations regarding the addition of SMA are common to all conditions that may be considered for addition to the NNBSP. They are not discussed in detail in this HTA.
- The benefit – harm balance of screening may differ depending on the survival motor neuron 2 *(SMN2)* copy numbers of the detected SMA case.
    - Were current treatment access arrangements in Ireland to hold in the context of screening being in place, those with fewer than four copies of *SMN2* (the majority of patients with SMA) would likely benefit from a screening programme for SMA as they would have earlier access to treatment, which is likely to lead to improved clinical outcomes. However, as *SMN2* copy number is not fully concordant with SMA type, some patients within this grouping would not be expected to develop a severe type of SMA in the absence of treatment. Therefore, such patients could potentially receive a different treatment, or receive treatment earlier than would have been required, than in the absence of screening.
    - The benefit is expected to be more variable in the case of children with four or more copies of *SMN2*. These patients would likely be placed on a watchful waiting strategy. Such a strategy would lead to a reduction in the time to establish a definitive diagnosis and would facilitate monitoring for changes indicative of disease onset and progression. This would likely lead to earlier access to appropriate therapies than would occur in the absence of screening. However, there may be harms in terms of stress and anxiety for the individual and the family, as well as the possibility for disruption of family-child bonding.
    - Those with compound heterozygous variants of survival motor neuron 1 *(SMN1)* (2-5% of SMA cases) would not be detected by the screening test and would not benefit from a screening programme for SMA.

- With regards to autonomy, screening for SMA involves a particularly vulnerable population (newborns) with consent for screening and decision-making for care deferred to parents.
    - The informed consent process needs to be clear that SMA caused by compound heterozygous variants of *SMN1* will not be detected by the screening test. It is important that SMA is not considered to be ruled out, as a result of a 'not suspected' finding, and that cases that subsequently present symptomatically are not overlooked.
    - It is important to note that screening of newborns for SMA may further result in subsequent identification of other family members, particularly asymptomatic minors, as either being affected with SMA or as carriers.
    - Where a definition of screen positivity based on *SMN2* copy number is used, this could potentially imply non-disclosure of a genetic diagnosis of SMA to a subset of individuals. This must be counterbalanced by the challenges for parents and clinicians of disclosing genetic information that is of uncertain value.
- Healthcare budgets are finite. In the implementation of any technology, the financial resources for implementation must be found from within the existing health budget or from the wider public sector budget. Consideration must be given to the ethical issues arising from the discontinuance or re-allocation of existing services, within the context of equity and justice for all patients. This is particularly relevant when considering the cost of the disease-modifying treatments for SMA, and the uncertainties that exist in the estimates of the cost effectiveness and budget impact of adding screening for SMA to the NNBSP.
- In terms of the ethical consequences relating to the conduct of the HTA itself, there are limitations in the evidence available nationally and internationally. The evidence relating to clinical outcomes of a screening programme for SMA is inherently linked to the clinical outcomes of the disease-modifying treatments. Therefore, the impact of the screening programme in isolation is difficult to discern.

8.1 Introduction

The purpose of this chapter is to describe the ethical and social considerations associated with the potential addition of spinal muscular atrophy (SMA) 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.[224] 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 HTA itself (for example, the time at which a HTA is conducted).

An ethics workshop was undertaken where members of HIQA's HTA Directorate discussed these issues. The findings of this workshop were supplemented by a review of relevant literature. 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 (that is, providing benefits and balancing benefits against risks and costs)
- autonomy (that is, respecting the decision-making capacities of an autonomous person)
- respect for persons (that is, an individual's privacy, integrity and dignity)
- justice and equity (that is, fairness in the distribution of benefits, risks, and costs)
- ethical consequences of the HTA (that is, the considerations relating directly to conducting the assessment at this time).

Some ethical and social considerations for the addition of SMA will be common to all conditions that may be considered for addition to the NNBSP. These have been thoroughly outlined and discussed previously in a previous HTA of the addition of severe combined immunodeficiency disease (SCID) to the NNBSP (link).[10] While they are briefly mentioned in this report at the beginning of each of the topics, they are not discussed again in detail.

8.2 Benefit – harm balance

As is the case for all rare diseases which may be considered for addition to the NNBSP, universal screening for SMA involves offering testing to all newborns in order to identify a small number of children with SMA (an average of 6.5 cases annually; 95% prediction interval: 2 to 13 cases, based on international data; see chapter 3). 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.[224] As the addition of SMA would constitute an expansion of an existing screening programme focused on rare diseases, ethical concerns specifically regarding the testing of a large population to detect a small number of cases would not be considered to be overly contentious in the context of this HTA.

The following sections will consider the potential benefits and harms of the addition of SMA to the NNBSP for all children screened, for children with SMA and their families, as well as the perceptions and expectations of families of those with SMA, patients with SMA, and healthcare providers.

8.2.1 Children screened for SMA

Any requirement for a separate blood draw to perform confirmatory testing may represent a potential harm of screening as families may be contacted for what is subsequently confirmed as a false positive result. However, if confirmatory testing can be undertaken on the original bloodspot sample taken for the purpose of newborn screening, a separate blood draw would not be required. Decisions on sample requirements (blood spot or a separate venous blood draw) would be taken at the laboratory verification stage prior to implementation of screening. In any case, based on the evidence from existing screening programmes implemented internationally, examined in chapter 4, the number of children incorrectly identified by the screening test who would require confirmatory testing to resolve this is expected to be very small (fewer than 6 children per year); of 16 studies examined, ten reported no false positive results.

8.2.2 Children with SMA

While it is important to note that every screening test has some risk of false negatives, the instances of these are extremely low in the case of the proposed method of newborn bloodspot screening for SMA. As noted in chapter 4 (clinical effectiveness of screening), the positive predictive value (PPV) of the screening test for SMA is high. In studies identified in the review of clinical effectiveness of screening (chapter 4), the midpoint PPV was 100%, and the false positivity rate was less than 0.01% in all but one study. Therefore, there is a high degree of confidence that when an infant is screened with the result being positive for SMA, or as 'SMA not suspected', this accurately reflects a case of SMA, or the lack of presence of SMA, respectively. However, the screening test does not identify cases of SMA caused by compound heterozygous variants of survival motor neuron 1 *(SMN1)* (see chapter 2: description of technology).

As discussed in chapters 4 (clinical effectiveness of screening) and 5 (overview of treatments), there are likely clinical benefits of early identification to the child with SMA. SMA can be associated with significant morbidity and mortality due to progressive and irreversible destruction of nerve cells in the brain and spinal cord.

Early detection potentially enables earlier access to treatment, ideally in the presymptomatic phase prior to neuronal loss. No trials to date have directly compared presymptomatic initiation of treatment to symptomatic initiation of treatment. However, there is limited evidence to suggest that earlier treatment may be associated with greater improvement in functional outcomes and reduced morbidity compared with later treatment (see chapter 5: overview of treatments).[187, 191]

However, it is important to note that the benefit is expected to be more variable for some patients with SMA, depending on their survival motor neuron 2 *(SMN2)* copy number. It is unclear whether patients with four or more copies of *SMN2* would be able to avail of immediate treatment in the context of screening, (see chapter 5: overview of treatments). A small number of patients would likely be put on a watchful waiting strategy based on their *SMN2* copy number, which may be appropriate management. However, although most patients identified with four or more copies of *SMN2* will present with symptoms later and with less severe types of SMA, there will be cases that present earlier and with a more severe type of SMA than predicted from the *SMN2* copy number. There may still be benefits to earlier identification for these patients;[146] they would likely benefit clinically from a watchful waiting strategy where they are regularly monitored for changes indicative of disease onset and progression. Also, early identification may lead to benefits in terms of a reduced diagnostic odyssey (meaning, a reduction in the uncertain and often unpredictable time from initial presentation with clinical symptoms suggestive of a person's condition to receiving a definitive diagnosis).[258] The condition would have already been identified, therefore when symptoms do present, the patient with SMA would likely be able to receive appropriate treatment and support sooner than if they were to present with no known prior diagnosis of SMA. This can also be beneficial to the family, as the diagnostic journey and associated uncertainty and wait period can be associated with stress and anxiety for the family.[258] It is noted that screening is not, however, a substitute for optimising diagnostic pathways for children presenting with neuromuscular symptoms.

It is also important to highlight the potential harms to patients with SMA. Cases of SMA identified through screening are at a higher risk of overtreatment, especially those with higher *SMN2* copy numbers. There is the possibility that some patients with SMA who may be treated early may not have presented with a severe type of SMA, and therefore they may receive treatment that would not be appropriate for their case, or earlier than would have been otherwise recommended. For example, while two *SMN2* copies are commonly seen in type I SMA (see chapter 3: epidemiology), other SMA subtypes may also present with this genotype, that is, it is possible that they may have a later onset form of SMA that would not have required early or the same treatment. This potential for over-medicalisation could result in

harms for the patient due to treatment-related adverse events and for the patient and their family in terms of psychological distress. There may also be implications for the healthcare system, as further discussed below under 'Justice and Equity'.

It is also important to consider that the test is designed only to detect homozygous deletions of *SMN1* (see chapter 2: description of technology). While homozygous deletions of *SMN1* account for approximately 95-98% of SMA, the condition can also be caused by compound heterozygous variants (2-5% of SMA), whereby one copy of the gene is absent and the other has experienced some form of pathogenic variant, inhibiting its ability to produce the spinal motor neuron protein. This genotype will not be identified through the newborn bloodspot screening programme. As a result, individuals with this genotype, despite having SMA, will not benefit from the introduction of newborn bloodspot screening for SMA and will be identified through the current standard of care (that is, identification through clinical signs).

Furthermore, there should be consideration given to the impact of labelling a person with SMA prior to their becoming symptomatic. There may be psychological concerns for the child as there may be a prolonged duration before becoming symptomatic (up until adulthood for those with type IV SMA). Regular follow-up in order to monitor SMA progression may also cause disruption to the individual's daily life.[146] In a recent survey of parents of children identified with SMA through a pilot of newborn screening in Germany, the authors identified a high sense of 'social burden' at greater than 12 months post newborn screening, despite only a few children in the cohort being severely affected.[259] Here, families feared negative effects of the disease in their child in relation to the family's employment and participation in social life. The authors speculated that patients with SMA detected through newborn screening are perceived by their parents as chronically ill children, even where they showed almost normal motor development under treatment.

Additionally, there is the possibility for disruption of the initial family-child bonding, as some parents may find it difficult to bond with a child they are aware may become ill.[260, 261] Surveys published in 2017 and 2018 (before the widespread availability of disease-modifying treatments) found that 26% of respondents from the general population (n = 232), 32% of respondents who were adults with SMA (n = 175), and 48% of respondents of families of patients with SMA (n = 61) agreed that identifying SMA before symptoms emerge would prevent families and children enjoying life while they are symptom free.[233, 262, 263] Only 13% of respondents from the general population, 15% of respondents who were adults with SMA, and 15% of respondents of families of patients with SMA agreed that identification of SMA at birth would interfere with the early bonding process.[233, 262, 263]

8.2.3 Cascade testing

Once a patient with SMA is identified, there is the possibility for cascade testing (that is, the testing of family members for a genetic condition following identification of an index case) (see chapter 4: clinical effectiveness of screening). This testing may have benefits in terms of identification of other SMA cases allowing for monitoring of the identified cases for symptoms of disease progression. It is important to note that cases identified through cascade testing (as with those identified by newborn bloodspot screening) may have an unclear disease progression. Additionally, due to their older age at identification there may not be the same treatment options for a patient identified with SMA through cascade testing compared to those that may be offered to a patient identified through newborn bloodspot screening. Identified cases would be able to access genetic counselling, and would have information to enable reproductive decision-making.

Cascade testing may result in the identification of carriers. Suggested benefits include that they would be able to access genetic counselling, and would have information to enable reproductive decision-making. However, carrier identification may also cause distress and adversely affect the reproductive choices of these individuals concerned. While carrier identification may represent a potential benefit or harm arising from SMA screening, the identification of carriers is not an aim of screening.

8.2.4 Perceptions and expectations of newborn bloodspot screening for SMA

In Ireland, there is a high level of participation in the NNBSP. This is suggestive of a certain level of confidence and or trust in the programme itself. In terms of acceptability of newborn bloodspot screening for SMA, a 2018 survey of the general population of the UK found that 84% of survey participants (n = 196) would support newborn bloodspot screening for SMA.[233]

While the general population may have certain expectations regarding the introduction of newborn bloodspot screening for SMA, it is also important to consider the expectations and opinions of those who are impacted by the condition, both directly (individuals with SMA) and indirectly (family members of those with SMA). Surveys which were conducted in the UK and published in 2017 demonstrated that even before disease-modifying treatments were available, individuals and family members of those with SMA were largely in favour of screening for the condition.[262] Overall, 74% (n = 61) of respondents with SMA and 69% (n = 175) of respondents of families of those with SMA were noted as being in favour of newborn bloodspot screening for the condition.[262] Reasons for supporting screening included better support for children and families (84%, n = 282) as well as the potential to enrol in clinical trials (74%, n = 251). Of those who were not in favour of screening, one

reason cited was the lack of available treatment.[262] Therefore, in the advent of currently available treatments, there is potential for increased favourability for newborn bloodspot screening in both of these groups. Notably, across all three groups (general population, individuals with SMA, and families of those with SMA), newborn bloodspot screening for SMA was only considered unethical by between 6 to 10% of participants (depending on the respondent group).[233, 262]

A more recent 2021 Australian study, which examined the perspectives of parents (n = 29) and healthcare professionals (n = 15) in a pilot programme for newborn bloodspot screening for SMA, found that the programme had a positive impact on the psychological well-being of both parents and healthcare professionals involved.[155] All parents affected by a positive screening result reported that they would participate in future newborn bloodspot screening programmes for SMA, indicating a high level of satisfaction with the pilot. Perceived benefits by parents for taking part in the programme included 'cherishing their child and family', 'early access to management options', 'potential of better clinical outcomes and facilitating the diagnostic journey for the family', while potential disadvantages noted were 'the fear for the future' and 'potential for stigmatisation'. Perceived benefits by the healthcare professionals included 'enabling early diagnosis and implementation of intervention strategies' and 'equitable diagnosis and accessing health resources within a personalised model of care'. Challenges noted by the healthcare professionals included 'managing the timing of information provision, assessment, and intervention', 'understanding, translating and relating unexpected findings' and 'managing uncertainty associated with using predictive screening tests'. The representativeness of these results to cases with higher copy numbers who are expected to develop less severe disease is unclear. Initially, the Australian study applied a screening threshold for positivity of less than four copies. At a later date, the program changed their definition to capture all cases with a homozygous *SMN1* deletion regardless of *SMN2* copy number. Only one case in the study held four or more *SMN2* copies.

It is important to note that while newborn bloodspot screening for SMA may enable earlier treatment, this does not amount to a cure for the condition. In a recent survey of parents of children identified with SMA through a pilot of newborn screening in Germany, the authors observed a desire of many families to change treatment strategy from nusinersen, a treatment which is to be given regularly until no longer tolerated, to onasemnogene abeparvovec, a one-off gene therapy.[259] While the reasons underlying this are unknown, it was speculated that this may be interpreted as a desire for a 'solution' to the disease, that is, to avoid the permanent stress of a chronic disease with chronic need for medication. The authors suggested that parents of children diagnosed with SMA should be prepared from the outset

that newborn bloodspot screening for SMA will change the natural course of the disease to become a treatable chronic disease.

8.3 Autonomy

As noted in the HTA of the addition of screening for SCID to the NNBSP,[10] several considerations related to autonomy should be acknowledged. These include the vulnerability of the target population. 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. There is also the potential for information overload in the initial days after the birth of their child. This information overload may be compounded by the inclusion of additional conditions being added to the NNBSP, as each condition will have unique aspects for the parents to consider. However, it is important to note that consent for the NNBSP includes testing for all conditions and there is no option to opt out of certain tests.

This section will describe the following considerations for autonomy of the addition of SMA to the NNBSP: informed consent, shared decision-making, testing of asymptomatic siblings, and the disclosure of results with higher copy numbers.

8.3.1 Informed consent

While there are general considerations for informed consent for the NNBSP, there are also considerations specific to SMA. As previously noted, compound heterozygous variants of *SMN1* will not be detected by the newborn bloodspot screening method (see chapter 2: description of technology). It is important that this is clearly communicated during the informed consent process to ensure that this is understood.[144] Additionally, there is the possibility for a false sense of security in that if the patient does present symptomatically, SMA may not be considered as a possible diagnosis if there is a lack of awareness of the compound heterozygous variants of *SMN1* not being detected through newborn bloodspot screening.

For some SMA cases identified, the only available intervention may be watchful waiting. Consideration should be given to including information within the informed consent process on the availability of treatment options in the event of a child being identified as a case. This may depend on the definition of screen positivity used.

8.3.2 Shared decision-making

In Ireland, parents have responsibility for decision-making regarding care for their child. The parents have the right to choose whether or not their child with SMA receives treatment. As noted in chapter 4 (clinical effectiveness), some parents did initially refuse treatment, and then subsequently changed their mind and requested treatment for their child.[52, 147] The initial refusal may impact which treatment the child is eligible for (for example, if they are past the age of eligibility or have become

symptomatic). This may then have an impact on the outcomes for the child. Treatment may be initiated more promptly in some cases if the child has symptoms of SMA, compared to the case of an asymptomatic child identified through screening.

While some diagnoses of SMA may result in an almost immediate initiation of treatment, for others the treatment pathway may be less clear. For the parents of these children, there may be a sense of anxiety and a preference to begin treatment as soon as possible. This could result in parents of a child with a diagnosis of SMA requesting treatments which are not indicated or available in the case of their child's clinical status.

A 2021 Australian study examined the perspectives of parents and health professionals involved in a pilot newborn bloodspot screening programme for SMA. This study highlighted the importance of shared decision-making and the provision of information between healthcare professionals and families, even when disease-modifying treatments were not initiated.[155] This may suggest that future programmes should prioritise open communication and collaboration between healthcare professionals and families to ensure that families feel supported and informed throughout the screening and treatment process.

8.3.3 Testing of asymptomatic siblings

Genetic testing needs to be considered in terms of the individual's right to know their SMA status. As previously stated, if an infant is identified as having SMA, there is then the possibility for cascade testing, where other family members can be tested. Additionally, carriers may be unintentionally identified due to the autosomal recessive inheritance pattern of SMA. This can have an impact on the autonomy of the individual, where they may not have the choice to choose for themselves whether to be identified (as either cases or as carriers). In the case of asymptomatic siblings in Ireland, generally, they will receive neuromuscular assessments, and then genetic testing if there are any signs or symptoms of SMA (see chapter 2: description of technology). Regardless, these individuals will likely continue to be monitored, which impacts on their right to choose, even though they were not identified through newborn bloodspot screening.

The European Society of Human Genetics suggests that genetic testing should be discouraged in asymptomatic individuals who may have conditions that cannot be treated or prevented until the individual has the maturity to comprehend the implications and make an informed decision.[264, 265] While disease-modifying treatments are available for many cases of SMA, as previously noted, some cases may not be eligible for these treatments, and SMA is not preventable. Therefore, according to these criteria, testing for SMA should be discouraged until the asymptomatic minor has the capacity for informed decision. However, due to the homozygous recessive inheritance pattern of SMA resulting from homozygous

deletion of exon 7 of the *SMN1* gene, when an infant is identified as having SMA by a screening programme, their asymptomatic sibling is immediately known to have a 25% chance of being affected with SMA and a 50% chance of being a carrier, impacting their right to decide themselves whether to know and/or have this risk information disclosed.

8.3.4 Disclosure of results with higher copy numbers (definition of screen positivity)

Screening programmes in different countries differ in what is considered a screen positive result for SMA.[42, 43, 54-57] While most international SMA newborn bloodspot screening programmes do not include *SMN2* copy numbers as a cut-off for screen positivity, of the 20 countries identified with some form of screening programme in place, two programmes were identified that do (see chapter 2: description of technology). In some Canadian screening programmes (provinces of Alberta, British Columbia, Manitoba, and Ontario), only individuals with homozygous deletions of *SMN1* and who have four or fewer copies of *SMN2* are considered be a positive result,[42] while in Sweden, a criterion for being considered screen positive is having three or fewer copies of *SMN2*.[43] A working group from Ontario considered that the natural history of patients with five or more copies of *SMN2* was not wholly predictable and concluded that reporting the condition, when disease manifestation may not occur, was unethical and not in the patient's best interest. This conclusion was made in light of the potential psychosocial impact, exclusion from insurance, and other potential ramifications associated with disclosure.[47] The programme in Sweden also considered that the natural history of symptom development in those with four or more copies of *SMN2* is unclear, and therefore the appropriate treatment for these individuals is also unclear.[43]

The results for those with *SMN2* copy numbers higher than the screen positive cut-off criteria in those programmes are not disclosed to the individual or their families. Careful consideration is needed regarding disclosure of results, especially in the instance of higher *SMN2* copy numbers. As previously noted, and as described in chapter 3 (epidemiology), higher copy numbers of *SMN2* are often seen in milder and later onset types of SMA; however, this is not always the case and some may present earlier and with more severe types.

Regardless of whether or not there are immediately available treatments, the patient does still have a form of SMA. Under a human rights-based approach to healthcare, considering core ethical expectations regarding patients' rights, including informed consent and access to their health information, patients and their families may feel they have a 'right to know', especially given the affected patient would likely present with symptoms at some point in their life. The merits of a definition of SMA positivity that does not depend on an *SMN2* cut-off include ending the diagnostic odyssey for

patients with screen-detectable SMA, providing access to health information that has been gathered as part of newborn screening, and enabling ongoing monitoring in order to facilitate faster access to treatment, should this be necessary. However, for patients with SMA genotypes indicative of less severe disease, it must be acknowledged that diagnostic labelling and watchful waiting may be associated with psychological distress for affected patients and their families. As previously noted, a 2021 Australian study examined the perspectives of parents (n = 29) in a pilot programme of newborn screening for SMA. This study found that on receiving a screen-positive result, the majority of parents reported that they had experienced anxiety (83%), in some cases with concomitant anger (14%), sadness (14%), and/or confusion (34%).[155]

The potential for overtreatment of patients must also be considered. Diagnosis does not necessarily result in better clinical outcomes for all patients identified by screening. Overtreatment may unnecessarily expose patients to potential harms associated with pharmacological treatment, contribute to inefficient use of finite healthcare resources, and may threaten the sustainability of healthcare systems due to rising disease management and treatment costs.[266]

8.4 Respect for persons

The EUnetHTA Core Model[224] 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 (for example, the privacy and rights of an asymptomatic sibling). These aspects have been considered throughout the chapter (for example, see section 8.3.3), and no additional ethical or social arguments were identified relating to 'respect for persons' for the addition of screening for SMA to the NNBSP.

8.5 Justice and equity

As previously noted in the report for the addition of SCID to the NNBSP,[10] there are some key concerns relevant to all conditions that may be considered for addition to the programme. First, as noted above, provision of consent for newborn bloodspot screening is deferred to the parent of the child. Therefore, the perceptions of the parent directly influence the ability of the child to access screening. These perceptions can be influenced by elements such as trust in healthcare, health literacy, prior experience, and individual beliefs.[261] However, it is important to note that screening for SMA may be considered to be an equitable undertaking in that the NNBSP in Ireland is a voluntary programme which is offered to the parents of all newborns.

This section will describe the following considerations for justice and equity of the addition of SMA to the NNBSP: healthcare resource use and alternative timings of screening for SMA.

8.5.1 Healthcare resource use

As with the addition of SCID,[10] and as identified in chapter 6 (systematic review of cost effectiveness) and chapter 7 (organisational and budgetary implications), there are uncertainties as to the cost effectiveness and budget impact of adding screening for SMA 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.

If interventions are implemented despite not being cost effective, this represents an inefficient use of resources. In implementation of any technology, the financial resources for implementation must be found from within the existing health budget or from the wider public sector budget. Consideration must therefore be given to the ethical issues arising from the discontinuance or re-allocation of existing services, within the context of equity and justice for all patients.

Additionally, individuals with SMA identified through screening would likely enter the healthcare system earlier than in the absence of screening. As previously stated, if current treatment access arrangements in Ireland were to hold in the context of screening being in place, those with three or fewer copies of *SMN2* would likely have access to treatment immediately. These cases are likely to be a considerable driver of costs to the system, which are important to consider in light of a finite budget (see chapter 7: organisational and budgetary implications).

Further, there would likely be higher demand on diagnostic testing, such as multiplex ligation-dependent probe amplification and genetic testing for other family members, with further demand placed on clinical capacity.

8.5.2 Carrier and prenatal screening

While the focus of this HTA is newborn bloodspot screening for SMA, it is also important to consider other potential types of screening (see chapter 2: description of technology). Firstly, while molecular genetic testing can establish carrier status for SMA for a member of the general population, this is often not definitive in that only a risk of being a carrier can be provided (see section 3.1.2 for a detailed discussion of the limitations of carrier testing); additionally, in Ireland, carrier testing is typically only undertaken in the case of a positive family history. Of note though, carrier testing cannot be used as an absolute prediction for having a child with SMA even in the case of a positive family history, as cases of SMA can still occur even if carrier testing does not suggest a risk (see chapter 3: epidemiology). Additionally, as previously noted, a child with SMA may have *de novo SMN1* pathogenic variants in

one allele; in these instances, only one parent is a carrier.[2, 5] The risk of occurrence for such cases would not be identified via carrier testing of potential parents. Secondly, prenatal testing, which is typically performed when both parents are identified as carriers, can occur, most commonly through invasive collection of samples from the placenta at weeks 11 to 14 (chorionic villus sampling).[3, 33] These screening options can allow for planning for families prior to conception in the case of carrier testing, and prior to birth in the case of prenatal testing.[267] This may allow for similar benefits to newborn bloodspot screening, where the child can be identified and diagnosed with SMA early. As noted however, some cases of SMA will be missed by these methods. Regardless, both options may allow for the possibility of genetic counselling.

8.6 Ethical consequences of the HTA

This section will describe the following considerations for the ethical consequences of the HTA itself, namely the availability of evidence at the time of the HTA and the timing of the HTA.

8.6.1 Availability of evidence

As highlighted throughout this HTA, the rarity of SMA results in limitations in the available evidence nationally and internationally to inform these types of assessments. Although a pilot study of screening for SMA in Australia was identified,[153] the evidence related to clinical outcomes of a screening programme for SMA is inherently linked to the evidence related to clinical outcomes of disease-modifying treatments. Therefore, the impact of the screening programme in isolation is difficult to discern. Additionally, given that the disease-modifying treatments are considered relatively new, the long-term benefit is largely unknown.

The treatments are highly costly and a large proportion of the research into the effectiveness of both screening and treatment with the disease-modifying treatments is funded by the pharmaceutical companies manufacturing the treatments. This is important to note with respect to the potential for bias as these companies may derive benefit from screening programmes due to the inherent link between identification through screening and treatment. If more individuals are identified through screening than would be identified in its absence, there may be more cases eligible for disease-modifying treatments. Therefore, the pharmaceutical companies may benefit from having a larger pool of potential individuals eligible for treatment; this may lead to conflicts of interest in the conduct and reporting of research.

8.6.2 Timing of the HTA

The testing platform for SMA screening uses the same technology as SCID screening (which was approved for addition to the NNBSP in January 2023). Should screening

for SMA be recommended, this presents an opportunity for multiplex screening for the two conditions (that is simultaneously test for both conditions using the same testing platform) (see chapter 7: organisational and budgetary implications). Therefore, many of the cost and or organisational issues would be reduced for SMA (in comparison to a scenario of introduction of screening for SMA in the absence of screening for SCID), given much of the equipment, staffing, and training would already be in place.

The introduction of newly available disease-modifying treatments for SMA makes an assessment of the screening technology relevant for decision making. However, should the decision be made to introduce SMA to the NNBSP, it will likely not be implemented until construction of the new children's hospital, where the laboratory in which testing would likely be carried out is housed, is complete.[86] While this does not lessen the importance of the assessment, the introduction of this technology is contingent on the completion of the new hospital, and therefore delays in the completion of the hospital would directly impact the timeliness of implementation of newborn bloodspot screening for SMA.

8.7 Discussion

The purpose of this chapter was to outline the ethical and social considerations associated with the addition of screening for SMA to the NNBSP in Ireland. The considerations outlined are framed in the context of relevant norms, values, and current practices, with the aim of understanding the consequences of implementing or not implementing such a screening programme. As indicated in Appendix Chapter 1 ('NSAC Criteria by HTA domain), the present chapter supports consideration of the extent to which SMA meets NSAC criteria for the appraisal of a screening programme: these include, for example, the criterion 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 the benefit – harm balance, screening for SMA requires consideration of the different *SMN2* copy numbers that may be detected through screening. The benefit – harm balance differs across SMA types and *SMN2* copy numbers. If current treatment access arrangements in Ireland were to hold in the context of screening being in place, those with fewer than four copies of *SMN2* (the majority of patients with SMA) would likely benefit from a screening programme for SMA as they would have earlier access to treatment, which would be expected to lead to improved clinical outcomes. The benefit is expected to be more variable in the case of children with four or more copies of *SMN2*. The potential for over-treatment could result in harms for the patient due to treatment-related adverse events. Screening for SMA will have no benefit for those with SMA caused by compound heterozygous variants

of *SMN1*, as these cases will not be detected by the screening method. Screening also has the potential for benefits for both the parents, and family of the child involved in terms of a reduction in the diagnostic odyssey and the potential for cascade testing. However, there may be harms in terms of the possibility for disruption of family-child bonding, and the psychological distress for families associated with a diagnosis.

In terms of autonomy, consideration would need to be given to communicating that the screening test does not detect cases of SMA caused by compound heterozygous variants of *SMN1*. Parents have the responsibility for decision-making regarding their child's care and treatment, and there have been cases noted where treatment was initially refused followed by a change of mind and request for treatment. This can impact the child's eligibility for certain treatments and the child's outcomes. Additionally, due to the autosomal recessive inheritance pattern for SMA, consideration is needed for the autonomy and 'right to know or not to know' for family members that may be intentionally or unintentionally identified as carriers or cases. Furthermore, given that differences have been noted internationally,[42, 54-57] consideration should be given to the ethical consequences of disclosure versus non-disclosure of cases of SMA identified with higher copy numbers.

From the perspective of justice and equity, while the implementation of screening for SMA may represent an equitable investment considering all newborns are offered screening, there are wider concerns with respect to the equitable allocation of healthcare resources across the overall healthcare system.

If interventions are implemented despite not being cost effective, this represents an inefficient use of resources. When implementing any technology, the associated financial resources must be found from within the existing health budget or from the wider public sector budget. Consideration must therefore be given to the ethical issues arising from the discontinuance or re-allocation of existing services, within the context of equity and justice for all patients.

There are limitations in the available evidence nationally and internationally to inform this HTA. Evidence for the impact of screening is inherently linked to the clinical outcomes of the disease-modifying treatments, which are themselves relatively new, with unknown long term clinical benefit. Therefore, the impact of a screening programme for SMA in isolation is difficult to discern. Furthermore, there are important considerations for the timing of the HTA such as the recent recommendation for screening for SCID, which presents an opportunity to multiplex screening for the two conditions. Additionally, it is important to consider the ongoing construction of the new children's hospital where the laboratory testing is likely to be carried out, and the ongoing expansion of the newborn bloodspot screening programme.

While the ethical and social considerations outlined are important in decision-making, they are not unique to Ireland. Assessments carried out in Canada (Quebec) and the Netherlands have highlighted similar considerations.[14, 268] In both countries, while the ethical and social considerations were noted, screening for SMA was recommended, with consideration to these issues given during the decision-making process.

9 Discussion

9.1 Introduction

In January 2023, at the request of NSAC, HIQA agreed to undertake a HTA of the potential addition of spinal muscular atrophy (SMA) to the National Newborn Bloodspot Screening Programme (NNBSP). 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 HTA overall. This chapter also presents a discussion of considerations specifically in relation to the definition of screen positivity, as may be defined by *SMN2* copy number threshold.

9.2 Summary of key findings

The NSAC have produced a list of 20 criteria for appraising the viability, effectiveness and appropriateness of a screening programme (Appendix Chapter 1, Table A1.1); these are grouped under five headings: the condition, the screening method, the intervention, the screening programme, and implementation criteria.[231] The main findings from this report are presented below in the context of these criteria.

The condition

Per the NSAC criteria, the condition should be an important health problem.[231] SMA is a rare genetic neuromuscular disorder characterised by irreversible degeneration of motor neurons in the spinal cord resulting in progressive muscle wasting and weakness. As highlighted in chapter 2 (description of technology), SMA presents across a gradient of severity, traditionally classified clinically into five functional subtypes, types 0 to IV.[2, 3, 5] The most severe subtype, type 0, is generally not a target for intervention under a potential screening programme as it presents symptomatically at birth and is expected to be managed with supportive and palliative care. Types I to IV, however, are typically asymptomatic at birth, and, in the absence of newborn bloodspot screening, clinical suspicion of SMA is based on symptomatic presentation or family history. Type I SMA represents over half of all cases of SMA. This group is of particular importance given the rapid onset and severity of symptoms. In contrast, individuals with type IV SMA, that is, adult-onset disease, experience mild to moderate symptoms, can walk, and have a normal life expectancy. Despite the initiation of treatment at diagnosis (see 'The intervention' below), however, affected patients with types I to III SMA may still have significant issues with motor development. Also, given the recent availability of disease-modifying treatments, there remains substantial uncertainty regarding the long term outcomes of individuals who initiated treatment when symptomatic.

If screening were implemented, most patients would be identified prior to symptom onset. Establishing the likely prognosis of the patient (that is the expected phenotype), which in turn would inform treatment decisions, would rely on using the patient's genotype, specifically the survival motor neuron 2 *(SMN2)* gene copy number, as a biomarker. While lower copy numbers are typically associated with more severe SMA subtypes (and, conversely, higher copy numbers are typically associated with less severe disease), this correlation is not absolute.[2, 22] There is, for example, a proportion of patients with type I SMA who have four or more copies of *SMN2*, and, vice-versa, a proportion among type IV with two or three copies. This therefore complicates the management of those identified through screening, as it is not possible to predict with certainty which patients will develop severe disease. In section 9.4, the implications of limiting the aim of newborn screening to be to identify a specific subset of SMA patients are discussed.

As described in chapter 3, the estimated incidence of SMA based on international data is 1 in 8,932 (95% prediction interval 1 in 24,423 to 1 in 4,394). Available national data are broadly consistent with international figures, although the lack of centralised reporting of all SMA cases in Ireland presents challenges for interpretation. The incidence of SMA is within the range of incidence reported for the conditions currently screened for in the NNBSP; this extends from 1 in 155,200 (maple syrup urine disease) to 1 in 2,300 (each of congenital hypothyroidism and cystic fibrosis). Given the relatively recent introduction of newborn screening for SMA in other jurisdictions, it is difficult to assess the impact of screening on SMA incidence, that is, whether it ultimately results in an increase in the total number of cases that are identified.

It is important to note that screening may have implications for members of the screened newborn's family in terms of identifying SMA carrier status. While carriers are not identified directly from screening, the identification of a positive SMA case may lead to the earlier and increased identification of carriers among close family members of the positive case; this has ethical implications, for example, in relation to such individuals needing to consider the impact on their family planning. The potential requirement for psychological and genetic counselling supports for these individuals will need to be considered in the context of existing service capacity, should screening be implemented.

Overall, the SMA population in Ireland represents a small, but clinically important group. Despite substantial improvements in treatment outcomes in recent years with the availability of new disease-modifying treatments, an unmet need remains relating to the morbidity that patients still experience despite treatment.

The screening method

NSAC criteria for the screening method state that the method should be simple, safe, precise, reliable, and validated.[231] As noted in chapter 4, the positive predictive value of the SMA newborn bloodspot screening test is high, and the chance of false negatives is low. In the context of newborn screening, it may be possible for confirmatory testing to be completed using the bloodspot sample obtained for the purposes of newborn screening, so no additional blood draws are required and the family of the newborn is only contacted in the context of a positive confirmatory test. Additionally, there are no known incidental findings that can arise from the screening test. However, it is important to note that the screening test is only designed to detect homozygous deletions of *SMN1*, and therefore cases of SMA arising from compound heterozygous variants of *SMN1* will not be detected (between 2 to 5% of the total SMA cases).

While the screening method would detect all cases of homozygous deletions of *SMN1*, quantification of the *SMN2* copy number would be required to establish the expected prognosis and to inform treatment decisions.[2, 5, 17, 18] The testing method would therefore identify cases with homozygous survival motor neuron 1 (*SMN1)* deletion and their *SMN2* copy number (typically one to six). As highlighted above, *SMN2* copy number is not 100% concordant with the SMA type;[2, 22] as such, clinical decision-making based on *SMN2* copy number may not be fully reliable. Nonetheless, *SMN2* copy number has been used in some screening programmes to define screen positivity such that only those with fewer than a certain number of *SMN2* copies (such as three, or four) are notified as having a positive screening result for SMA. International examples of where such a screen positivity cut-off has been identified, and the underpinning rationale for using such a cut-off, are summarised below in section 9.3. There are significant implications associated with basing a screen positivity cut-off on *SMN2* copy number; considerations for decision-making on this topic are summarised in section 9.4.

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.[231] NSAC criteria also specify that there should be agreed evidence-based policies covering which individuals should be offered interventions and the appropriate intervention to be offered.[231] In the context of a screening programme for SMA being introduced in Ireland, a working group of stakeholders, including clinical specialists, would need to be established to outline the associated pathways, including the treatment pathway. A treatment pathway would be influenced by the most up-to-date evidence with

respect to treatment effectiveness and the access arrangements for the relevant treatments at that time, in addition to factors relating to patient experience. It is important to note that treatment of SMA may change substantially in the coming years as further evidence emerges.

With respect to availability, as of August 2023, three disease-modifying treatments have been licensed by the European Medicines Agency (EMA).[29-31] At present, at least one treatment is available within the publicly funded healthcare system in Ireland (that is, it is reimbursed by the HSE) for patients who are presymptomatic with up to three *SMN2* copies, subject to the terms of a HSE managed access protocol. While treatments are available for SMA, funding arrangements have not been agreed in the context of screening. Such access would need to be clarified.

As is the case for many rare diseases, very limited evidence is available from clinical trials to determine whether presymptomatic or early treatment leads to better outcomes compared with usual care. This is not surprising given there are ethical challenges associated with the initiation of such studies in patients who have few copies of *SMN2* given the progressive nature of the disease and the expected benefit of treatment. In the absence of direct evidence from randomised controlled clinical trials, it was necessary to consider lower quality sources of evidence. Given the gradient of severity observed with SMA, the expected benefit of screening varies by clinical type. The quality of evidence also differs between types. As noted previously, in the absence of screening, around 50% of patients are estimated to present with type I SMA. Of these, a considerable proportion of cases have two copies of *SMN2*. In patients with two *SMN2* copies, there is evidence, though limited, that earlier treatment initiation is more beneficial than later initiation for both patients who are presymptomatic or symptomatic at the time of treatment initiation.[163, 191] It is expected that the benefits observed in patients with two *SMN2* copies can be extrapolated to those patients with three *SMN2* copies who would develop type I SMA in the absence of disease-modifying treatments. It is important to note, however, that some patients may still experience motor dysfunction even if treatment is initiated when they are presymptomatic.[163]

While limited evidence was found, there is high clinical plausibility for a benefit associated with earlier treatment compared to treatment initiated on diagnosis following clinical presentation; this is due to the progressive nature of SMA and the potential to reduce neuronal loss.[123] However, given the limitations of the available evidence, it is not possible to quantify this potential benefit. While clinical plausibility indicates that research is worth pursuing, it cannot replace the research itself. The impact of earlier treatment can be further explored indirectly by examining studies that look at the clinical effectiveness of screening. These studies are discussed under 'The screening programme' heading below.

Despite the encouraging evidence regarding the benefits of earlier treatment initiation, there are many knowledge gaps. Importantly in the context of screening, there is a lack of comparative effectiveness data for the timing and choice of disease-modifying treatments. Screening may be expected to lead to an increased number of patients being administered onasemnogene abeparvovec (OA). These additional patients predominantly reflect those who would be expected to develop type II or type III disease and who otherwise (that is, in the absence of screening) would be treated with nusinersen or risdiplam following a clinical diagnosis. Given the lack of appropriate comparative effectiveness data, the clinical impact of this shift in treatment assignment is uncertain. Also, while these patients represent a minority of those who would be identified through screening, most of the financial impact of screening is attributable to this group. While the historic proportions of individuals that develop type I, II and III disease are known, it is not currently possible to identify with any certainty which asymptomatic SMA cases would develop each of these types in the absence of treatment.

Knowledge gaps are more substantial for patients with either one or four copies of *SMN2*. For such patients, neither single-arm nor comparative trial data were identified to determine the efficacy of disease-modifying treatment in the presymptomatic setting. No patients with one copy, and only one patient with four copies, was included in the screened cohort of the single comparative outcome study identified.[153] Those with five or more copies rarely present in the clinical setting.

For patients identified through screening as having four or more copies of *SMN2*, watchful waiting is an important management option. Given the anticipated increased recognition of SMA symptoms in those with a diagnosis of SMA compared with those who are not known to have the condition,[163] screening would still be expected to reduce the time to treatment initiation and therefore potentially lead to improved outcomes. There is, however, no international guidance on the level of monitoring required or the point at which treatment should be initiated in this group, as well as concerns regarding the applicability of available clinical trial evidence to this population, and to the screening context.

In the face of considerable uncertainty regarding the benefits of presymptomatic intervention in patients with higher *SMN2* copy numbers, a watchful waiting strategy has been proposed. This would represent a potential means of minimising the risk of irreversible disease progression in patients with discordant genotypes and phenotypes (that is, patients with higher *SMN2* copy numbers who may present with early-onset disease). While such a strategy would identify those at risk of developing severe disease, it could be argued that the potential harms in terms of psychological distress may outweigh the benefits for some patients, including those who never present with symptoms and those who experience disease progression after 18 years of age, for whom no pharmacological treatment options are currently available

in Ireland. Watchful waiting strategies have been used in clinical practice in other contexts where the disease evolves slowly over time and may never cause any problems for the patient (for example, prostate cancer). However, where used in clinical practice, it is often in adult populations.[269] The decision to implement a watchful waiting strategy in the context of newborn screening is more complex, as the decision is made on behalf of a child who may never benefit from the intervention and will have to cope with the diagnosis for the rest of their life.

As of August 2023, treatments are only available in Ireland for those who meet treatment initiation criteria before the age of 18 years; that is, there are no disease-modifying treatment options for those who experience adult-onset (type IV) disease. However, it is not possible to determine with any certainty which individuals would develop type IV disease based on their genotype alone. There are a number of issues with respect to those with type IV disease. First, if screening is implemented, individuals who would otherwise not become aware of their condition until adulthood would have the psychological burden of having a genetic SMA diagnosis. Given they are infants at the time of screening, they would have lost autonomy with respect to the decision to be tested for SMA. In terms of management, there is a risk of overtreatment if treatment is initiated early and in the absence of symptoms. Alternatively, these individuals may be managed with watchful waiting for all of their childhood, but if they become symptomatic as adults, based on current criteria they would not have access to disease-modifying treatment. In noting this, it is likely that the treatment landscape will substantially change over time with the potential that treatment options may become available for those with adult-onset disease. Further, while based on historic data this group is estimated to represent approximately 1% of the total SMA population, it is not known if screening leads to an increase in the total number of individuals with diagnosed SMA. Any increase in incidence would most likely represent detection of those with mildly symptomatic disease, such as patients with type IV SMA, who may have remained undetected in a no-screening scenario. Therefore, it is not possible to reliably determine the size of this cohort.

The screening programme

NSAC criteria for the screening programme state that ideally there should be evidence from high quality randomised controlled trials that the screening programme is effective in reducing mortality or morbidity.[231] Evidence relating to the effectiveness of screening for SMA was identified by way of a systematic review of international literature of approaches and outcomes of newborn bloodspot screening for SMA (chapter 4). As previously noted, a limited number of studies were identified that compared the clinical outcomes for screened and unscreened cohorts.[130, 133, 137] One study explicitly compared outcomes in a screened cohort with an unscreened cohort and suggested significantly improved outcomes with screening.[153] In line with the expected epidemiology, only one patient in both

cohorts had four *SMN2* copies, which limits the applicability of the results to this cohort. While this study suggests a potential positive impact of screening on morbidity, it is important to recognise that the effects observed were inherently linked to the effectiveness of the treatments themselves, and not the screening programme itself in isolation. Furthermore, as highlighted in chapter 5, evidence on long-term outcomes of treatment is lacking.

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.[231] In terms of acceptability, there is a high level of participation in the NNBSP in Ireland.[232] This is suggestive of a certain level of confidence and or trust in the programme. Evidence from surveys conducted in the UK suggests that screening for SMA is acceptable to both the general public, and affected patients and their families, even in an era before the widespread availability of disease-modifying treatments.[233, 262] As discussed in chapter 8, with the introduction of screening for SMA, the benefit – harm balance of screening would likely differ depending on the *SMN2* copy numbers of the detected SMA case. This benefit – harm balance is challenging to predict in the context of a screening programme as *SMN2* copy number is not fully concordant with the SMA type.

Further 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.[231] If interventions are implemented despite not being cost effective, this represents an inefficient use of resources. When implementing any technology, the associated financial resources must be found from within the existing health budget or from the wider public sector budget. Consideration must therefore be given to the ethical issues arising from the discontinuance or re-allocation of existing services, within the context of equity and justice for all patients.

The evidence relating to the cost effectiveness of screening for SMA was based on a systematic review of economic evaluations. In the absence of robust clinical data inputs, published economic evaluations adopted diverse approaches to estimating the cost effectiveness of newborn bloodspot screening for SMA relative to clinical presentation, leading to heterogeneous results, ranging from not cost effective to cost-saving.[205-208] As discussed in chapter 6, there is also potential for the authors' conflicts of interest, particularly in relation to funding sources, to influence the interpretation of the study findings. Evidence gaps, including uncertainty associated with the applicability of available utility values, limited evidence for asymptomatic individuals, an absence of long-term clinical effectiveness data, and a lack of evidence for those with higher copy numbers present considerable challenges for reliable estimation of the cost effectiveness. As a result, the cost effectiveness of

screening is subject to considerable uncertainty. In particular, the available evidence suggests that the cost effectiveness of newborn bloodspot screening for SMA is highly dependent on the choice of disease-modifying therapy following a positive screening test result. Given insufficient evidence to inform reliable estimation of the cost effectiveness of screening in the Irish setting, de novo modelling to inform cost effectiveness of screening in the Irish setting was not undertaken. As new evidence emerges, unbiased, objective economic evaluations will be important to provide clarity regarding to cost effectiveness of screening for SMA.

The affordability of adding SMA to the SMA to the NNBSP was assessed by way of a budget impact analysis. Considering the first five years of the programme (one year of verification pre-implementation and four years of screening), the total incremental budget impact to implement screening for SMA was estimated at approximately €17.7 million (95% confidence interval: €5.1 to €40.5 million). The majority (approximately 90%) of the costs were attributable to earlier diagnosis and subsequent pharmacological treatment of an estimated 25 patients. The estimated incremental budget impact was subject to considerable uncertainty in sensitivity and scenario analyses due to limited evidence underpinning key input parameters; these parameters included epidemiological data (for example the incidence and the proportion of patients with less than four *SMN2* copies), the cost of disease-modifying treatments, and knowledge gaps related to reimbursement criteria for available disease-modifying treatments.

The implications of screening for SMA must also be considered in terms of consequences for those exposed to cascade testing. Should the introduction of newborn screening for SMA result in the identification of additional cases above and beyond the current rate of diagnosis by clinical signs, the need for additional cascade testing may also increase. Similar to the concepts surrounding 'labelling' which were raised in chapter 8, additional cascade testing may result in the identification of family members who have SMA or who are carriers, for whom there is no clinical utility in receiving this information.

Implementation criteria

NSAC specify several criteria in relation to the implementation of a screening programme, including the clinical care pathway, staffing and resources, and quality assurance processes, among other factors.[231] As discussed in chapter 7, while there is potential for synergies in terms of laboratory resource consumption associated with the addition of SMA to the NNBSP (in the context of screening for SCID already being recommended), introduction of screening for SMA would not be without challenges. Delivery of the programme would likely be unfeasible prior to the opening of the laboratory at the new children's hospital owing to infrastructural limitations at the existing site of the National Newborn Bloodspot Screening

Laboratory (NNBSL); this may negatively influence time to implementation.[10, 86] Furthermore, the ongoing shortage of medical laboratory scientists across the public service has the potential to result in delays to implementation, or diversion of resources from existing activities.[247]

From a clinical perspective, at present, it is anticipated that capacity for monitoring, treatment and long-term follow-up could largely be delivered within existing resources, although investment could be required in the future in line with growth in the size of the patient cohort requiring long-term follow-up. It was noted, however, that the recruitment of a clinical psychologist would be required to provide support both patients and their families. Psychological support for patients and their families is a critical, but often overlooked, component of care.[270, 271] The introduction of screening may be associated with increased needs for psychological support due to the earlier identification of patients who may not have presented until later in life, in particular, for patients who enter a watchful waiting strategy. Where cases are identified through screening, cascade testing may identify SMA carriers among their family members. The requirement for additional genetic counselling resources to support these individuals will need to be considered in the context of the available service capacity. In terms of management pathways, while there is currently an established pathway providing end-to-end care for patients presenting symptomatically with SMA, if a decision were made to implement screening for SMA, this pathway would need to be reconsidered in light of the potential influence of changes in treatment assignment and timing of diagnosis on clinical pathways. Decision-making regarding the timing of treatment initiation and the treatment used would largely shift from being based on SMA type to being on the basis of *SMN2* copy number. Importantly, for some patients a watchful waiting strategy may be indicated on the basis of their *SMN2* copy number or may be preferred by the parents. In the absence of screening, processes for watchful waiting, including the frequency of follow-up and criteria for treatment initiation (for example, sub-clinical detection versus overt symptoms) have not been established. A standardised pathway for these patients would need to be developed as part of implementation planning.

9.3 Findings relative to international assessments

Several national and regional health organisations have previously completed assessments regarding the addition of screening for SMA to a newborn bloodspot screening programme; such assessments have been conducted in Sweden, Canada (Quebec), Germany, the Netherlands, the UK, and the US.[14, 268, 272-274] Authorities in Sweden, Canada (Quebec), the Netherlands, and Germany all recommended the addition of SMA. The report from the US provided an evidence summary, which was followed by a vote by the Health and Human Services' Advisory Committee on Heritable Disorders in Newborns and Children to add SMA to the US Recommended

Uniform Screening Panel. In 2018 the UK concluded there was not enough evidence for the UK NSC criteria to support a population-wide screening programme for SMA; however, this report was published prior to the availability of the disease-modifying treatments. The key findings and considerations from the reports in the context of the findings of this HTA are described below.

As discussed in chapter 8, the majority of screening programmes internationally do not include an *SMN2* copy number cut-off for screen positivity, although this has been applied in some contexts. A January 2023 report published by the National Board of Health and Welfare in Sweden, which informed a decision to implement screening, recommended that only those with three or fewer copies of *SMN2* be identified as a positive screening test result. The report noted that at the time of writing there was a lack of clarity regarding the benefit – harm balance among children with four copies of *SMN2,* however, expansion of screening to this group may be considered in the future as the evidence base develops.[43]

The report from Canada (Quebec), published in 2021, was broadly consistent with the findings of this HTA. It was highlighted that there were no studies identified that compared the outcomes for children screened for SMA and those not screened for SMA.[14] Consistent with our findings, it was noted that there was evidence to suggest that treatment administered early or presymptomatically appeared to be more effective in preventing death, in reducing the need for permanent ventilation and in resulting in improvements in motor outcomes compared with later initiation of treatment, after symptom onset. However, the authors noted that there was a lack of long-term treatment effectiveness data. The authors also considered the importance of the fact that the test analyses genetic material; in contrast to the Irish context, where testing for cystic fibrosis using genetic material is already in place as part of newborn screening (specifically during confirmatory testing), screening for SMA would be the first newborn screening testing in Quebec to use genetic material. An important consideration highlighted by the authors is that the testing method used does not involve genome sequencing, and is highly selective for *SMN1* and *SMN2* genes, which may lessen concerns. It was also noted that a centralised database relating to the screening and follow-up of identified cases would facilitate a better understanding of the SMA in the local context. Similarly, as noted in chapter 3, the absence of centralised epidemiological data collection in the Irish context presents challenges for estimation of incidence and prevalence. Consistent with the findings of this HTA, the authors also noted potential harms of the screening test relating to not identifying cases with compound heterozygous variants of *SMN1.* The need for collection of data to evaluate the impact of screening and early treatment, should screening be implemented, was further stressed. In contrast to the report from Sweden, the Quebec report did not define an *SMN2* cut-off for screen

positivity, although four provinces in Canada (Alberta, British Columbia, Manitoba and Ontario) have separately defined a *SMN2* cut-off number for screen positivity.

National level assessments were undertaken in Germany, the Netherlands, the UK and the US between 2018 and 2020.[268, 272-274] It is important to note that these assessments were subject to even greater limitations in the evidence base when compared with the current context (see section 9.4), due to recent developments in the treatment landscape, and subsequent changes in international practice in relation to screening. Therefore, the conclusions of these assessments should be considered in the context of the evidence available at the time of assessment.

While the treatment landscape has advanced rapidly in recent years, many of the challenges in relation to the underlying evidence identified in these assessments are still relevant to the current context. The report from the Netherlands, published in 2020, highlighted that, for some patients with SMA, there was a lack of clarity on optimal timing of treatment initiation, and that long-term consequences of treatment are unknown.[268] The authors also noted that treatment protocols would need to be developed, especially with regard to patients with four or more copies of *SMN2*, as they would not receive treatment immediately, based on the available treatments in the Netherlands at the time of analysis. The report from IQWiG in Germany, also published in 2020, suggested that there may be a benefit from newborn screening, relative to no screening; however, numerous knowledge gaps were identified, consistent with those highlighted previously.[272] In the current context, there is still uncertainty regarding the optimal treatment pathway for patients with four or more copies of *SMN2* due to the dearth of clinical trial evidence in this population.

In the US context, SMA was recommended for inclusion in the recommended uniform screening panel in 2018, following a vote by the Committee on Heritable Disorders in Newborns and Children. A review of changes in screening practices across the US, published in 2020, highlighted widespread adoption after SMA was added to the recommended uniform screening panel; 24 of the 53 state/territory programs reported full implementation.[275] Consistent with previous reports, the 2020 report highlighted the clinical pathway for patients with four or more copies of *SMN2* as particularly challenging. A further challenge highlighted by the report was the need to ensure the availability of clinical services for short- and long-term follow-up. Similarly, in the context of the current HTA, while it is anticipated the clinical capacity for monitoring, treatment and follow-up could be provided within existing resources, in the longer-term, review of available resources would be important in line with an increasing cohort of patients requiring follow-up, as noted in section 9.2.

Finally, the report from the UK published in 2018 did not recommend screening, based on the evidence available at the time of analysis.[274] However, the topic is currently under reconsideration.[219] As noted in chapter 6, existing cost-

effectiveness models are associated with considerable limitations. With cognisance of these limitations, the UK National Screening Service have recommended that a new cost-effectiveness model for the UK screening context be developed, and that scoping should commence on an in-service evaluation of newborn screening for SMA to inform the recommendations of the UK National Screening Service.[219] Separately, a pilot study by Oxford University, and funded by the pharmaceutical industry and academia, is currently underway as of March 2022, and is expected to be completed by March 2025. This study aims to evaluate the uptake and feasibility of population-based newborn bloodspot screening for SMA in four hospital trusts in the Thames Valley.[78, 276] In the design of the pilot study, careful consideration was given to ensuring that it does not interfere with the existing screening programme in any way, which currently has an uptake rate of over 99%.[277]

9.4 Considerations relating to the definition of screen positivity

As with all screening programmes, in contemplating the potential addition of SMA to the NNBSP, a decision must be made regarding the aim of screening. In considering the benefits and harms of a screening programme, it is recognised that the proper aim of screening is to identify those who will benefit from early detection.[278] This would exclude, for example, screening solely for the purpose of determining carrier status. Detecting, and thereby labelling, people who will not suffer adverse health outcomes, does not incur a clinical benefit, and is to be avoided under the principles of screening devised by Wilson and Jungner. Such detection could result in disbenefits, particularly where follow-up results in further investigations and potential treatments that may in themselves induce harm in the patient, physically, psychologically or otherwise.

Newborn screening represents a particular challenge in defining the target of screening in that identification of a rare genetic or congenital condition in a child results in labelling the child from the earliest stages of their development. This includes the neonatal period when family members may be particularly vulnerable to the psychosocial effects of the diagnosis. In the case of conditions such as SMA, which presents on a spectrum of increasing disease severity (from prenatal onset associated with early mortality, to adult-onset disease with a mild-to-moderate disease course), the potential to benefit from screening varies. While new disease-modifying treatments have become available which have the potential to significantly reduce morbidity and mortality, particularly if initiated prior to symptom onset, the condition is currently incurable. Irrespective of the potential to benefit, once a condition is identified, there are ethical arguments supporting its disclosure to the person even where there is a low probability of it presenting clinically in the short or medium term and or a low probability of early intervention resulting in improved clinical outcomes.

In the case of SMA, testing primarily involves identification of a homozygous deletion of *SMN1*; individuals in whom this deletion is identified through screening have a genetic diagnosis of SMA. The expected severity of SMA varies by *SMN2* gene copy number, with higher *SMN2* copy numbers typically associated with later-onset, less severe disease, although this correlation is not absolute. As those identified through newborn screening typically do not have symptoms, newborn screening by default identifies a genotype, but not a phenotype. Presently, there is no reliable alternative to *SMN2* copy number to predict the development of symptoms and sequelae.

The potential ethical consequences of identification of different genotypes of SMA are outlined in chapter 8 (ethical and social considerations). Given differences in the potential for benefit and for harm, one option is to limit the target of SMA screening to those at risk of more severe disease which presents in childhood (types I to III disease). Alternatively, it may be considered that the target of screening should be to identify only those for whom a treatment of proven clinical benefit is currently available. It should however be borne in mind that treatment availability may change over time as evidence emerges and or as managed access arrangements in place are adjusted, so the definition of screen positivity may require adjustment in line with changes in treatment availability. Where it is considered desirable to target a subset of all cases of SMA, in the absence of a valid alternative biomarker, the definition of screen positivity could be based on a stated maximum *SMN2* copy number (for example, ≤ 3 copies, ≤ 4 copies). This approach would recognise the correlation, albeit imperfect, between *SMN2* copy numbers and disease severity and uncertainty around the effectiveness (and therefore cost effectiveness) and or availability of treatment for those with higher *SMN2* copy numbers.

In two countries (Sweden and several regions in Canada), *SMN2* copy number is currently noted as being used as a cut-off for screen positivity. In Sweden, where a threshold of three or fewer copies of *SMN2* is being used to define a screen positive result, the rationale was based on the uncertainty of benefit in patients with higher copy numbers. In the Canadian regions of Alberta, British Columbia, Manitoba and Ontario, a threshold of four or fewer copies of *SMN2* is being used. This decision was reported to have been made in light of the uncertain natural history of patients with higher *SMN2* copy numbers and a lack of clarity regarding appropriate treatment for these individuals. No other current examples of use of an *SMN2* copy number threshold for screen positivity were identified in this HTA. It is important to note that a definition of screen positivity dependent on *SMN2* copy number would have ethical implications in addition to those with respect to the benefit-harm balance of screening for SMA overall. Such a practice could imply non-disclosure of a genetic diagnosis. While it may be possible to filter results such that no personnel have knowledge of the genetic result, this approach could still have implications for the rights of the person with a homozygous deletion of *SMN1* to be informed of this abnormal result.

Furthermore, given the high prevalence of carriers of the SMA gene, the absence of knowledge of a genetic diagnosis could impact the screened individual's ability to make properly informed reproductive choices, which may have serious implications. In Caucasian populations, approximately one in 46 are estimated to be carriers of the SMA gene. Where both parents are carriers, each of their children has a one in four chance of having SMA; where one parent is a carrier and the other has SMA, each of their children has a one in two chance of having SMA. While the rights of the person screened take precedence, where a child is diagnosed with SMA, there may also be cascade screening of their parents to identify carrier status and to inform future family planning. Were non-disclosure of results of a genetic diagnosis of SMA to take place, parents would not receive this information. While disclosing all results irrespective of the *SMN2* copy number would address the above ethical issues, this approach would need to be counterbalanced by the challenges for parents and clinicians of disclosing genetic information that is of uncertain value.

Given the implications of adopting a threshold for screen positivity, decision-makers should clarify whether the aim of screening should be to identify all cases of SMA resulting from a homozygous deletion of *SMN1* or to identify a subset of these cases, as indicated by an *SMN2* copy number threshold. This decision would be made in the context of a screening test which, in the absence of an *SMN2* threshold, detects approximately 95% of SMA cases, due to its inability to detect compound heterozygous variants.

Key considerations that may inform this decision include:

- Reliability of *SMN2* copy number in distinguishing cases of SMA that are most and least likely to benefit
    - While *SMN2* copy number is a prognostic indicator of severity (that is, of type), it is not fully reliable as a biomarker; a small minority of patients with higher copy numbers (for example, those with four *SMN2* copies) may present early in childhood and may incur significant motor neuron damage in the absence of early treatment. In a meta-analysis conducted for this HTA, based on historical data largely derived from a context without screening programmes:
        - 99.8% of those identified with up to three copies of *SMN2* were estimated to present with types I to III SMA.
        - 94% of those identified with four *SMN2* copies were estimated to present with types I to III.
        - Among those with five or more copies of *SMN2*, the likely clinical course in the absence of treatment is subject to substantial uncertainty, but is expected to represent mild SMA.

- Quantification of *SMN2* copy number on the basis of MLPA can be unreliable, with reliability influenced by various laboratory-based factors. Any decision to limit a definition of screen positivity may need to be contingent on the outcomes of a validation process for quantifying *SMN2* copy number in patients with higher copy numbers.

- The proportion of cases of SMA with higher copy numbers that would be identified with SMA through newborn screening
  - Based on historical data largely derived from a context without screening programmes, those with four or more *SMN2* copies are estimated to represent 15% of cases, while those with five or more copies of *SMN2* represent 3.9% of cases.
  - It is possible that screening may result in an increased percentage of cases having higher copy numbers due to increased identification of those who are asymptomatic or who have mild disease who would otherwise go undetected.
  - Given an estimated international incidence of 1 in 8,932 births and a birth rate of 58,000 births per annum, over a ten year period, 65 cases of SMA would likely be detected through screening. Given the historical data above, on average, fewer than 10 of these cases would have four or more copies of *SMN2* of which fewer than three cases would have five or more copies of *SMN2.*

- Treatment availability for those with higher *SMN2* copy numbers
  - Those with three or fewer copies of *SMN2* may be expected to have earlier access to disease-modifying treatments under screening; for example, onasemnogene abeparvovec is currently reimbursed in Ireland for SMA patients with up to three *SMN2* copies, subject to conditions of a managed access protocol. Existing access arrangements to reimbursed treatments were devised in the context of no screening being in place.
  - It is unlikely that patients with higher *SMN2* copy numbers (for example, five copies) would be offered treatment at this time as there is a lack of evidence regarding the effectiveness of treatments in such patients. In the event of a decision to implement screening for SMA, treatment pathways would need to be devised to clarify exactly which groups of patients would be eligible for disease-modifying treatment versus a watchful waiting strategy followed by treatment initiation upon symptom development.

- The expected benefit-harm balance associated with early identification of cases of SMA with different numbers of *SMN2* copies
    - Patients with a lower copy number of *SMN2* often develop a more severe and early onset of disease. Therefore early identification and early access to disease-modifying treatments is expected to have the most benefit in these patients.
    - Patients with a higher copy number of *SMN2* typically develop a less severe disease, with later onset of disease. Therefore these patients may not benefit as much from early identification due to the risk of medicalisation or overtreatment which may be distressing to both cases identified and their families. If identified through screening, such patients may not have immediate access to disease-modifying treatments, and may be placed on a watchful waiting strategy to monitor for changes indicative of disease onset and progression.
- The cost effectiveness of screening in the case of different scenarios of an *SMN2* copy number threshold being used to define screen positivity
    - While a de novo economic evaluation was not undertaken in this HTA, a systematic review of published studies identified substantial variability in the estimated cost effectiveness of screening for SMA; this was due to differences in the methodological approaches adopted and the treatment landscape at the time of analysis. In included studies, the distribution of *SMN2* copy number in the screened cohort was based on the results of international screening programmes, which at the time of analysis had largely reported data for patients with four or fewer copies of *SMN2* only. There are insufficient epidemiological and clinical data to support subgroup analysis according to alternative definitions of screen positivity. As such, the cost effectiveness of screening for SMA overall is highly uncertain, and the cost effectiveness of screening specifically in a cohort with greater than four copies of *SMN2* is unknown. While it is plausible that cost effectiveness of screening may vary according to the genotype detected, it is noted that patients with higher *SMN2* copy numbers likely represent a small proportion of all cases with SMA (as above, historical data suggest 3.9% with five or more *SMN2* copies).
- The budget impact associated with identification of different subsets of patients with SMA
    - Identification from the point of a positive screening test result of patients who would otherwise be identified in late childhood or in

adulthood will result in absolute increases in healthcare costs as a result of increased medicalisation (including potential treatment) of such individuals.

- Impact of non-disclosure of a genetic diagnosis on the informed consent process and the integrity of the programme, bearing in mind considerations regarding the rights of an individual to knowledge regarding their test results, and associated impacts on reproductive choices (as noted above). This must be balanced against the impact of disclosure of results of uncertain significance to screened individuals and their families.

9.5 Strengths and limitations

The findings of this assessment should be considered in light of its overall strengths and limitations. In terms of strengths, a robust approach to the assessment was employed with publication of a protocol for the HTA,[198] and the establishment of an Expert Advisory Group (EAG) comprising a broad range of both national and international key stakeholders to provide expert input and advice. Furthermore, the HTA was conducted in accordance with national and international HTA guidelines.[197, 200, 224, 235] In line with these best practice guidelines, systematic review methodology was used to identify and summarise the available clinical and cost effectiveness literature, while adhering to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses criteria.[197] Although a de novo systematic review was not conducted to identify trials of disease-modifying treatment in the presymptomatic setting, a comprehensive overview was undertaken.

However, some important limitations exist in relation to the currently available evidence and the methodological approaches applied in this HTA, which must be considered in in the context of the overall findings. SMA is a rare disease, and, therefore, there are challenges associated with research relating to this condition. The majority of evidence to inform this assessment was derived from the international literature, which may limit the overall applicability to the Irish context. The available national data suggest consistency with international epidemiological trends, taking into account naturally occurring variation in the context of rare diseases and the potential for underdiagnosis of milder disease types.

Importantly, the impact of screening on outcomes for SMA is inherently linked to the effectiveness of the treatments themselves, and not the screening programme in isolation. Therefore, the direct impact of a screening programme is difficult to discern. Only one non-randomised study from Australia was identified that compared clinical outcomes in screened and unscreened cohorts.[153] In light of significant ongoing changes in international practice, with implementation at national, regional or pilot levels identified in 21 countries, as outlined in chapter 2, it is likely that

further evidence in relation to the outcomes of screening programmes will begin to emerge. The potential benefit of waiting for additional evidence to inform a decision on screening implementation should be balanced against the benefit - harm balance associated with a delayed implementation of screening. Another consideration relates to the fact that it may be easier to expand a screening programme when further evidence emerges than to withdraw or restrict a programme once it is implemented.

As noted, a de novo systematic review was not conducted to identify trials of disease-modifying treatment in the presymptomatic setting, though a comprehensive overview was undertaken. A recent systematic review in this area did not identify any additional trials to those identified within the comprehensive overview. However, this systematic review did include additional longer-term follow-up data that was made available through academic conferences, which was not included in the overview provided. These data have not been published in peer reviewed journals, which limits the ability of this HTA to include a critical appraisal of the findings. In any case, the authors' main findings of the systematic review have been included in this HTA.

As discussed, data regarding the effectiveness of disease-modifying treatment were limited in terms of follow-up and effectiveness has not been shown for all types of SMA (for example, in patients with presymptomatic SMA with one copy or four or more copies of *SMN2*). There was also limited evidence identified with respect to a potential treatment benefit for early versus later treatment initiation, making it challenging to discern the impact of screening and therefore the potential impact of presymptomatic treatment initiation. Finally, a large proportion of the research identified regarding the effectiveness of screening overall and of disease-modifying treatment was funded by manufacturers of SMA treatments, potentially introducing bias.

Although a de novo Ireland-specific economic evaluation would be the preferred approach to inform estimation of the cost effectiveness of a newborn screening programme for SMA, such an analysis was not considered feasible due to limitations in the evidence base at the time of analysis. Due to the lack of Irish data, a de novo Ireland-specific cost-utility analysis would likely rely on input parameters from existing analyses. Therefore, reliable estimation of the cost effectiveness of a newborn bloodspot screening programme for SMA relative to no screening in the Irish context would be challenging.

In order to inform consideration of the economic consequences associated with screening, a budget impact analysis was undertaken, given the importance of affordability to policymakers.[279] The budget impact analysis was estimated using the publicly available list price of the available disease-modifying treatments. The net

drug acquisition costs are anticipated to be lower than the publicly available list price but this cannot be confirmed due to the confidential nature of the agreements.[167, 174, 175] To account for this uncertainty, scenario analyses were conducted to examine the impact of alternative prices on the estimates. Furthermore, as the budget impact analysis estimates costs over a short-term time horizon, consistent with national HTA guidelines, the results cannot capture the potential for a reduced total spend per patient associated with potential treatment reassignment in the context of screening. However, short-term time horizons are more relevant to national budgeting cycles, and are subject to less uncertainty when compared with extrapolation of data over longer-term time horizons. Finally, it is important to note that the clinical care pathway modelled for the purposes of the budget impact analysis was developed in consultation with clinical experts, based on the available evidence at the time of analysis. Due to the rapidly advancing nature of the treatment landscape, if a decision were made to implement screening for SMA, the treatment pathway would need to be considered in the context of the evidence available at the time of implementation. This pathway would require ongoing refinement in line with changes in best practice recommendations and the evolving needs of service users over time. Although the budget impact analysis produced wide-ranging results, owing to the considerable uncertainty associated with key input parameters due to the rarity of the disease, it is important to note that this reflects the best available estimate of the uncertainty associated with the incremental budget impact. The magnitude of this uncertainty must be considered by decision-makers.

9.6 Conclusion

SMA is a rare genetic neuromuscular disorder characterised by significant morbidity and mortality. The condition results in irreversible degeneration of motor neurons in the spinal cord leading to progressive muscle wasting and weakness and occurs across a gradient of severity. The proposed screening method accurately identifies homozygous deletions of the *SMN1* gene which are associated with at least 95% of cases of SMA. It will not detect cases of SMA that do not involve homozygous *SMN1* gene deletion (2-5% cases). If newborn bloodspot screening were implemented, many cases would be identified prior to symptom onset. Based on limited data, there is evidence to suggest that screening, compared with no screening, is associated with clinical benefits due to earlier identification and access to care for those who would otherwise develop type I to type III disease. However, due to the absence of complete correlation between *SMN2* copy number and SMA type, it is not possible to predict with certainty which patients will develop severe disease. As such, the benefit – harm balance in the context of screening varies across individuals. Furthermore, introduction of screening would likely be associated with a change in treatment practices, and therefore a considerable increase in pharmacological expenditure in the short-term. With regard to treatment availability, at least one

treatment is available within the publicly funded healthcare system in Ireland (that is, reimbursed), for patients who are presymptomatic and have up to three *SMN2* copies. However, funding arrangements have not been agreed in the context of screening. Such access would need to be clarified.

Given the variable expected benefit-harm balance of screening for patients with different numbers of *SMN2* copies, and the complexities of treatment availability, a decision to recommend screening should specify whether the aim is to identify all cases of SMA resulting from a homozygous deletion of *SMN1* or to identify the subset of cases most likely to develop clinically significant disease. A definition of screen positivity may be devised based on *SMN2* copy number such that only those with SMA who have a copy number within a certain range are disclosed as being screen positive. There are potential ethical issues that would arise from limiting identification to a subset of cases on the basis of *SMN2* copy number. These include a risk of harm in children who could otherwise have been identified through screening, given that *SMN2* copy number is an imperfect biomarker of severity. However, this risk would need to be balanced against the ethical implications of identifying babies as having a condition in the absence of a clear correlation between genotype and phenotype. The potential benefits of a screening programme, comprising end-to-end care, need to be considered in light of key uncertainties including the epidemiology of SMA types in Ireland, a rapidly evolving treatment landscape, a lack of long-term effectiveness data and uncertainty regarding reimbursement criteria in the context of screening. These knowledge gaps combine to produce significant uncertainty regarding the cost effectiveness and affordability of screening. In light of these uncertainties, ongoing monitoring of the outcomes of a screening programme for SMA would be important, should a decision be made to recommend screening.

References

1. Mercuri E, Finkel RS, Muntoni F, Wirth B, Montes J, Main M, et al. Diagnosis and management of spinal muscular atrophy: Part 1: Recommendations for diagnosis, rehabilitation, orthopedic and nutritional care. Neuromuscul Disord. 2018;28(2):103-15.
2. Wirth B, Karakaya M, Kye MJ, Mendoza-Ferreira N. Twenty-five years of spinal muscular atrophy research: from phenotype to genotype to therapy, and what comes next. Annual review of genomics and human genetics. 2020;21:231-61.
3. Keinath MC, Prior DE, Prior TW. Spinal Muscular Atrophy: Mutations, Testing, and Clinical Relevance. Appl Clin Genet. 2021;14:11-25.
4. Mercuri E, Pera MC, Scoto M, Finkel R, Muntoni F. Spinal muscular atrophy—insights and challenges in the treatment era. Nature Reviews Neurology. 2020;16(12):706-15.
5. Prior TW, Leach ME, Finanger E. Spinal muscular atrophy. 2020. In: GeneReviews [Internet]. Seattle: University of Washington. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1352/.
6. Carter M, Tobin A, Coy L, McDonald D, Hennessy M, O'Rourke D. Room to improve: The diagnostic journey of Spinal Muscular Atrophy. European Journal of Paediatric Neurology. 2023;42:42-6.
7. Dangouloff T, Vrščaj E, Servais L, Osredkar D, Adoukonou T, Aryani O, et al. Newborn screening programs for spinal muscular atrophy worldwide: Where we stand and where to go. Neuromuscular Disorders. 2021;31(6):574-82.
8. Department of Health. National Screening Advisory Committee: NSAC criteria [Internet]. Dublin: Department of Health; 2020 [cited 2023 September 01]. Available from: https://www.gov.ie/en/publication/c0d9f8-about-the-national-screening-advisory-committee/#nsac-criteria.
9. National Screening Advisory Committee. Work programme - Proposed Modifications to Existing Screening Programmes [Internet]. Dublin: Department of Health; 2023 [cited 2023 April 14]. Available from: https://www.gov.ie/pdf/?file=https://assets.gov.ie/245481/c1564807-c01f-4923-b1ce-69779a51f7b6.pdf#page=null.
10. Health Information and Quality Authority. Health Technology Assessment of the addition of severe combined immunodeficiency (SCID) to the National Newborn Bloodspot Screening Programme [Internet]. Dublin: Health Information and Quality Authority; 2023 [cited 2023 March 14]. Available from: https://www.hiqa.ie/sites/default/files/2023-01/HTA_addition_of_SCID_to_NNBSP_Jan-2023.pdf.
11. Depatment of Health. National Screening Advisory Committee: Recommendations [Internet]. Dublin: Department of Health; 2021 [cited 2023 January 04]. Available from: https://www.gov.ie/en/publication/5af1dd-national-screening-advisory-committee-recommendations/.
12. Singh RN, Howell MD, Ottesen EW, Singh NN. Diverse role of survival motor neuron protein. Biochim Biophys Acta Gene Regul Mech. 2017;1860(3):299-315.

13. Dangouloff T, Vrscaj E, Servais L, Osredkar D, Group SNWS. Newborn screening programs for spinal muscular atrophy worldwide: Where we stand and where to go. Neuromuscul Disord. 2021;31(6):574-82.
14. Institut national d'excellence en santé et en services sociaux. Assessment of the suitability of neonatal screening for spinal muscular atrophy [Internet]. Québec: Gouvernement du Québec; 2021 [cited 2023 September 12]. Available from: https://www.inesss.qc.ca/fileadmin/doc/INESSS/Rapports/Depistage/INESSS_Amyotrophie_spinale_Avis.pdf.
15. Jedrzejowska M. Advances in Newborn Screening and Presymptomatic Diagnosis of Spinal Muscular Atrophy. Degener Neurol Neuromuscul Dis. 2020;10:39-47.
16. Chaytow H, Huang YT, Gillingwater TH, Faller KME. The role of survival motor neuron protein (SMN) in protein homeostasis. Cell Mol Life Sci. 2018;75(21):3877-94.
17. Butchbach ME. Copy number variations in the survival motor neuron genes: implications for spinal muscular atrophy and other neurodegenerative diseases. Frontiers in molecular biosciences. 2016;3:7.
18. Butchbach ME. Genomic variability in the survival motor neuron genes (SMN1 and SMN2): Implications for spinal muscular atrophy phenotype and therapeutics development. International Journal of Molecular Sciences. 2021;22(15):7896.
19. Schorling DC, Pechmann A, Kirschner J. Advances in Treatment of Spinal Muscular Atrophy - New Phenotypes, New Challenges, New Implications for Care. J Neuromuscul Dis. 2020;7(1):1-13.
20. Peeters K, Chamova T, Jordanova A. Clinical and genetic diversity of SMN1-negative proximal spinal muscular atrophies. Brain. 2014;137(11):2879-96.
21. Verhaart IE, Robertson A, Wilson IJ, Aartsma-Rus A, Cameron S, Jones CC, et al. Prevalence, incidence and carrier frequency of 5q–linked spinal muscular atrophy–a literature review. Orphanet journal of rare diseases. 2017;12(1):1-15.
22. Calucho M, Bernal S, Alías L, March F, Venceslá A, Rodríguez-Álvarez FJ, et al. Correlation between SMA type and SMN2 copy number revisited: an analysis of 625 unrelated Spanish patients and a compilation of 2834 reported cases. Neuromuscular Disorders. 2018;28(3):208-15.
23. Wang CH, Finkel RS, Bertini ES, Schroth M, Simonds A, Wong B, et al. Consensus statement for standard of care in spinal muscular atrophy. Journal of child neurology. 2007;22(8):1027-49.
24. Schorling DC, Becker J, Pechmann A, Langer T, Wirth B, Kirschner J. Discrepancy in redetermination of SMN2 copy numbers in children with SMA. Neurology. 2019;93(6):267-9.
25. Department of Molecular Genetics. Personal communication with HIQA. 2023.
26. Children's Health Ireland Consultant Paediatric Neurologist (Clinical Specialist SMA). SMA diagnosis and treatment in Ireland: Personal communication with HIQA. 2023.
27. Consultant Neurologist Tallaght. Information request: Personal communication with HIQA. 2023.

28. Finkel RS, Mercuri E, Meyer OH, Simonds AK, Schroth MK, Graham RJ, et al. Diagnosis and management of spinal muscular atrophy: Part 2: Pulmonary and acute care; medications, supplements and immunizations; other organ systems; and ethics. Neuromuscular Disorders. 2018;28(3):197-207.
29. European Medicines Agency. Spinraza [Internet]. Amsterdam: European Medicines Agency; 2023 [cited 2023 August 24]. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/spinraza.
30. European Medicines Agency. Evrysdi [Internet]. Amsterdam: European Medicines Agency; 2023 [cited 2023 September 25]. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/evrysdi/
31. European Medicines Agency. Zolgensma [Internet]. Amsterdam: European Medicines Agency; 2023 [cited 2023 August 24]. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/zolgensma.
32. American College of Obstetricians and Gynecologists. Carrier Screening for Genetic Conditions [Internet]. Washington: American College of Obstetricians and Gynecologists; 2017 [updated 2023; cited 2023 March 14]. Available from: https://www.acog.org/clinical/clinical-guidance/committee-opinion/articles/2017/03/carrier-screening-for-genetic-conditions.
33. National Health Service (NHS). Spinal Muscular Atrophy [Internet]. NHS; 2020 [cited 2023 August 24]. Available from: https://www.nhs.uk/conditions/spinal-muscular-atrophy-sma/diagnosis/.
34. Children's Health Ireland Consultant Clinical Geneticist. Diagnostic pathway for SMA in Ireland: Personal communications with HIQA. 2023.
35. National Newborn Bloodspot Screening Programme. Developement of pathways in the context of newborn screening: Personal communication with HIQA. 2023.
36. Children's Health Ireland at Temple Street. A Practical Guide to Newborn Bloodspot Screening In Ireland: 9th edition [Internet]. Dublin: Children's Health Ireland; 2022 [cited 2023 August 24]. Available from: https://www.hse.ie/eng/health/child/newbornscreening/newbornbloodspotscreening/information-for-professionals/a-practical-guide-to-newborn-bloodspot-screening-in-ireland.pdf.
37. ImmunoIVD. SPOT-it kit [Internet]. Stockholm: ImmunoIVD; 2023 [cited 2023 March 15]. Available from: https://www.immunoivd.com/trec-smn1.
38. PerkinElmer. EONIS Platform [Internet]. Waltham: PerkinElmer; 2023 [cited 2023 March 15]. Available from: https://rh.perkinelmer.com/products/eonis-system/.
39. Food and Drug Administration. PerkinElmer filings: Eonis [Internet]. Maryland: Food and Drug Administration; 2022 [cited 2023 March 15]. Available from: https://fda.report/Company/Perkinelmer-Inc.
40. Health Products Regulatory Authority. Guide to In-Vitro Diagnostic Medical Devices Legislation [Internet]. Dublin: Health Products Regulatory Authority; 2021 [cited 2023 March 15]. Available from: http://www.hpra.ie/docs/default-source/publications-forms/guidance-documents/sur-g0013-guide-to-in-vitro-diagnostic-medical-devices-legislation-v3.pdf?sfvrsn=8.
41. Medical Device Coordination Group. Guidance on Classification Rules for in vitro Diagnostic Medical Devices under Regulation (EU) 2017/746 [Internet]. Brussels: Medical Device Coordination Group,; 2023 [cited 2023 March 15].

Available from: https://health.ec.europa.eu/system/files/2023-02/md_mdcg_2020_guidance_classification_ivd-md_en.pdf.
42. Groulx-Boivin E, Osman H, Chakraborty P, Lintern S, Oskoui M, Selby K, et al. Variability in newborn screening across Canada: spinal muscular atrophy and beyond (P4-9.002). Can J Neurol Sci. 2023:1-7.
43. Socialstyrelsen. Spinal Muscular Atrophy (SMA) [Internet]. Sweden: Socialstyrelsen; 2023 [cited 2023 June 28]. Available from: https://www.socialstyrelsen.se/kunskapsstod-och-regler/regler-och-riktlinjer/nationella-screeningprogram/remissversioner/spinal-muskelatrofi/.
44. Glascock J, Sampson J, Haidet-Phillips A, Connolly A, Darras B, Day J, et al. Treatment algorithm for infants diagnosed with spinal muscular atrophy through newborn screening. Journal of neuromuscular diseases. 2018;5(2):145-58.
45. CureSMA. CureSMA [Internet]. CureSMA; 2023 [cited 2023 August 17]. Available from: https://www.curesma.org/.
46. Glascock J, Sampson J, Connolly AM, Darras BT, Day JW, Finkel R, et al. Revised Recommendations for the Treatment of Infants Diagnosed with Spinal Muscular Atrophy Via Newborn Screening Who Have 4 Copies of SMN2. J Neuromuscul Dis. 2020;7(2):97-100.
47. McMillan HJ, Kernohan KD, Yeh E, Amburgey K, Boyd J, Campbell C, et al. Newborn screening for spinal muscular atrophy: Ontario testing and follow-up recommendations. Canadian Journal of Neurological Sciences. 2021;48(4):504-11.
48. Kichula EA, Proud CM, Farrar MA, Kwon JM, Saito K, Desguerre I, et al. Expert recommendations and clinical considerations in the use of onasemnogene abeparvovec gene therapy for spinal muscular atrophy. Muscle & Nerve. 2021;64(4):413-27.
49. Medical University of Vienna. Neonatal screening: programme successfully expanded [Internet]. Vienna: Medical University of Vienna; 2022 [cited 2023 June 28]. Available from: https://www.meduniwien.ac.at/web/en/about-us/news/2022/news-in-june-2022/neugeborenen-screening-erweiterung-erfolgreich-umgesetzt/
50. Medical University of Vienna. Newborn screening [Internet]. Vienna: Medical University of Vienna; [cited 2023 June 28]. Available from: https://www.meduniwien.ac.at/hp/en/newborn-screening/.
51. Department of Health and Aged Care. What is screened in the program [Internet]. Canberra: Australian Government - Department of Health and Aged Care; [updated 2022 December 07; cited 2023 March 22]. Available from: https://www.health.gov.au/our-work/newborn-bloodspot-screening/what-is-screened-in-the-program.
52. Boemer F, Caberg J-H, Beckers P, Dideberg V, di Fiore S, Bours V, et al. Three years pilot of spinal muscular atrophy newborn screening turned into official program in Southern Belgium. Scientific reports. 2021;11(1):19922.
53. Vlaanderen. Newborn babies are now also screened for SMA [Internet]. Brussels: Vlaanderen; 2022 [cited 2023 August 17]. Available from: https://aangeboren.bevolkingsonderzoek.be/nl/aa/nieuws/pasgeboren-babys-worden-nu-ook-op-sma-gescreend.

54. Alberta Government. Alberta Newborn Screening Program [Internet]. Alberta: Alberta Government; [cited 2023 August 24]. Available from: https://www.alberta.ca/newborn-metabolic-screening.
55. Government of British Columbia. B.C. newborn screening expands; early detection improves quality of life [Internet]. British Columbia: Government of British Columbia; 2022 [cited 2023 March 22]. Available from: https://news.gov.bc.ca/releases/2022HLTH0197-001536.
56. Government of Manitoba. Province announces expansion of newborn screening program [Internet]. Manitoba: Government of Manitoba; 2022 [cited 2023 April 12]. Available from: https://news.gov.mb.ca/news/index.html?item=55077&posted=2022-06-08.
57. Newborn Screening Ontario. Spinal Muscular Atrophy (SMA) [Internet]. Ottawa: Newborn Screening Ontario; [cited 2023 March 22]. Available from: https://www.newbornscreening.on.ca/en/disease/spinal-muscular-atrophy-sma.
58. Saskatchewan Government. Saskatchewan Expanding Newborn Screening Program [Internet]. 2022 [cited 2023 June 22]. Available from: https://www.saskatchewan.ca/government/news-and-media/2022/february/23/saskatchewan-expanding-newborn-screening-program.
59. KBC Zagreb Hospital. Information for the public about newborn screening [Internet]. Zagreb: KBC Zagreb Hospital; 2023 [cited 2023 June 28]. Available from: https://www.kbc-zagreb.hr/informacije-javnosti-o-novorodjenackom-probiru.aspx.
60. University Hospital Motol. SCID and SMA neonatal screening project [Internet]. Prague: University Hospital Motol; 2022 [cited 2023 March 22]. Available from: https://www.fnmotol.cz/en/Press-Releases/neonatal-screening-project/.
61. Indenrigs- og Sundhedsministeriet. Nyfødte skal screenes for muskelsvind [Internet]. Copenhagen: Indenrigs- og Sundhedsministeriet; 2022 [updated 2022 October 4; cited 2023 March 22]. Available from: https://sum.dk/nyheder/2022/oktober/nyfoedte-skal-screenes-for-muskelsvind.
62. Statens Serum Istitut. New screening for spinal muscular atrophy [Internet]. Copenhagan: Statens Serum Istitut; 2023 [cited 2023 June 28]. Available from: https://nyfoedte.ssi.dk/.
63. Sarv S, Kahre T, Vaidla E, Pajusalu S, Muru K, Põder H, et al. The Birth Prevalence of Spinal Muscular Atrophy: A Population Specific Approach in Estonia. Frontiers in Genetics. 2021;12:2683.
64. Les Hopitaux Universitaires de Strasbourg. Lancement du projet depisma : La première étude pilote de dépistage néonatal génétique en france [Internet]. Strasbourg: Les Hopitaux Universitaires de Strasbourg; 2022 [updated 2022 June 24; cited 2023 April 12]. Available from: https://www.chru-strasbourg.fr/lancement-du-projet-depisma-la-premiere-etude-pilote-de-depistage-neonatal-genetique-en-france-2/.
65. Gemeinsamer Bundesausschuss. Kinder-Richtlinie: Neugeborenen-Screening auf 5q-assoziierte spinale Muskelatrophie [Internet]. Berlin: Gemeinsamer

Bundesausschuss; 2020 [cited 2023 March 22]. Available from: https://www.g-ba.de/beschluesse/4617/.
66. Országos Kórházi Foigazgatóság. Magyarországi házi gyermekorvosok, háziorvosok részére [Internet]. Budapest: Országos Kórházi Foigazgatóság; 2022 [cited 2023 March 22]. Available from: https://alapellatas.okfo.gov.hu/sma-szures/.
67. Unione Italiana Lotta alla Distrofia Muscolare. SMA: Presentato Lo Screening Neonatale Pilota [Internet]. Unione Italiana Lotta alla Distrofia Muscolare,; 2019 [cited 2023 March 22]. Available from: https://www.uildm.org/sma-presentato-lo-screening-neonatale-pilota
68. Puglia Salute. Screening obbligatorio per l'atrofia muscolare spinale (SMA) [Internet]. Bari: Regione Puglia Council; 2021 [cited 2023 August 24]. Available from: https://burp.regione.puglia.it/documents/20135/1504883/LR_04_2021.pdf.
69. Gailite L, Sterna O, Konika M, Isakovs A, Isakova J, Micule I, et al. New-born screening for spinal muscular atrophy: results of a Latvian pilot study. International Journal of Neonatal Screening. 2022;8(1):15.
70. Health Council of the Netherlands. Neonatal screening for spinal muscular atrophy [Internet]. The Hague: Health Council of the Netherlands; 2019 [cited 2023 March 22]. Available from: https://www.healthcouncil.nl/documents/advisory-reports/2019/07/23/neonatal-screening-for-spinal-muscular-atrophy.
71. Rijksinstituut voor Volksgezondheid en Milieu. From 1 June 2022, heel prick test also screens for muscle disease SMA, bringing number of screened diseases to 26 [Internet]. Bilthoven: Rijksinstituut voor Volksgezondheid en Milieu,; 2022 [cited 2023 April 12]. Available from: https://www.rivm.nl/en/news/from-1-june-2022-heel-prick-test-also-screens-for-muscle-disease-sma-bringing-number-of
72. New Zealand National Screening Advisory Committee. Minutes Wednesday 27 July 2022 [Internet]. Wellington: New Zealand National Screening Unit; 2022 [cited 2023 August 22]. Available from: https://www.nsu.govt.nz/system/files/page/nsac_27_jul_2022_minutes_final.pdf.
73. Oslo University Hospital. Nyfødtscreening [Internet]. Oslo: Oslo University Hospital; 2023 [updated 2023 March; cited 2023 March 22]. Available from: https://oslo-universitetssykehus.no/behandlinger/nyfodtscreening-blodprove-av-nyfodte/nyfodtscreening#sma-screening.
74. Instytut Matki i Dziecka. Badania Przesiewowe Noworodków [Internet]. Warsaw: Instytut Matki i Dziecka; [cited 2023 March 22]. Available from: http://przesiew.imid.med.pl/.
75. Portugese Neuromuscular Association. Inclusão da ame – atrofia muscular espinal no rastreio neonatal (teste do pezinho) [Internet]. Lisbon: Portugese Neuromuscular Association; 2022 [updated 2022 October 8; cited 2023 April 12]. Available from: https://apn.pt/apn/inclusao-da-ame-atrofia-muscular-espinal-no-rastreio-neonatal-teste-do-pezinho/.
76. Valencia University Hospital. La Fe will launch a pilot program of newborn screening to detect spinal muscular atrophy [Internet]. Valencia: Valencia University Hospital; 2021 [cited 2023 August 02]. Available from:

https://www.iislafe.es/en/whats-on/news/3163/la-fe-pondra-en-marcha-un-programa-piloto-de-cribado-neonatal-para-detectar-la-atrofia-muscular-espinal.
77. UK National Screening Committee. Antenatal and newborn screening programme - SMA [Internet]. UK: UK National Screening Committee; 2018 [cited 2023 March 22]. Available from: https://view-health-screening-recommendations.service.gov.uk/sma/.
78. University of Oxford - Department of Paediatrics. First UK pilot study of newborn screening for spinal muscular atrophy (SMA) launched in Oxford [Internet]. Oxford: University of Oxford; 2022 [cited 2023 March 22]. Available from: https://www.paediatrics.ox.ac.uk/news/first-uk-pilot-study-of-newborn-screening-for-spinal-muscular-atrophy-sma-launched-in-oxford.
79. The Advisory Committee on Heritable Disorders in Newborns and Children. Report to Congress [Internet]. Maryland: Health Resources and Services Administration; 2018 [cited 2023 August 24]. Available from: https://www.hrsa.gov/sites/default/files/hrsa/advisory-committees/heritable-disorders/reports-recommendations/2018-achdnc-report-congress.pdf.
80. Health Resources and Services Administration. Newborn Screening in Your State [Internet]. Maryland: Health Resources and Services Administration; [updated 2022 December; cited 2023 June 23]. Available from: https://newbornscreening.hrsa.gov/your-state.
81. D'Silva AM, Kariyawasam DS, Best S, Wiley V, Farrar MA, Group NSNS, et al. Integrating newborn screening for spinal muscular atrophy into health care systems: an Australian pilot programme. Developmental Medicine & Child Neurology. 2022;64(5):625-32.
82. Children's Health Ireland Consultant paediatric Neurologist (Clinical Specialist SMA). Historical cases of SMA in Ireland: Personal communication with HIQA. 2023.
83. Zlotogora J, Grotto I, Kaliner E, Gamzu R. The Israeli national population program of genetic carrier screening for reproductive purposes. Genetics in Medicine. 2016;18(2):203-6.
84. Department of Molecular Genetics. Summary data: Personal communication with HIQA. 2023.
85. Children's Health Ireland at Crumlin Clinical Scientist. Information request: Personal communication with HIQA. 2023.
86. National Newborn Bloodspot Screening Programme. Information request of requirements for newborn screening for SMA: Personal communication with HIQA. 2023.
87. Verhaart IE, Robertson A, Leary R, McMacken G, König K, Kirschner J, et al. A multi-source approach to determine SMA incidence and research ready population. Journal of neurology. 2017;264:1465-73.
88. Jędrzejowska M, Borkowska J, Zimowski J, Kostera-Pruszczyk A, Milewski M, Jurek M, et al. Unaffected patients with a homozygous absence of the SMN1 gene. European journal of human genetics. 2008;16(8):930-4.
89. Coratti G, Ricci M, Capasso A, D'amico A, Sansone V, Bruno C, et al. Prevalence of Spinal Muscular Atrophy in the Era of Disease-Modifying Therapies: An Italian Nationwide Survey. Neurology. 2023;100(11):522-8.

90. Kekou K, Svingou M, Sofocleous C, Mourtzi N, Nitsa E, Konstantinidis G, et al. Evaluation of genotypes and epidemiology of spinal muscular atrophy in Greece: a nationwide study spanning 24 years. Journal of neuromuscular diseases. 2020;7(3):247-56.
91. Wadman RI, Stam M, Gijzen M, Lemmink HH, Snoeck IN, Wijngaarde CA, et al. Association of motor milestones, SMN2 copy and outcome in spinal muscular atrophy types 0–4. Journal of Neurology, Neurosurgery & Psychiatry. 2017;88(4):365-7.
92. Jones CC, Cook SF, Jarecki J, Belter L, Reyna SP, Staropoli J, et al. Spinal muscular atrophy (SMA) subtype concordance in siblings: findings from the cure SMA cohort. Journal of neuromuscular diseases. 2020;7(1):33-40.
93. Lin L, Chu H. Meta-analysis of proportions using generalized linear mixed models. Epidemiology (Cambridge, Mass). 2020;31(5):713.
94. Pino MG, Rich KA, Kolb SJ. Update on biomarkers in spinal muscular atrophy. Biomarker Insights. 2021;16:11772719211035643.
95. Grotto S, Cuisset J-M, Marret S, Drunat S, Faure P, Audebert-Bellanger S, et al. Type 0 spinal muscular atrophy: further delineation of prenatal and postnatal features in 16 patients. Journal of neuromuscular diseases. 2016;3(4):487-95.
96. Pera MC, Coratti G, Berti B, D'Amico A, Sframeli M, Albamonte E, et al. Diagnostic journey in Spinal Muscular Atrophy: Is it still an odyssey? PLoS One. 2020;15(3):e0230677.
97. Souza P, Pinto W, Ricarte A, Badia B, Seneor D, Teixeira D, et al. Clinical and radiological profile of patients with spinal muscular atrophy type 4. European journal of neurology. 2021;28(2):609-19.
98. Lin C-W, Kalb SJ, Yeh W-S. Delay in diagnosis of spinal muscular atrophy: a systematic literature review. Pediatric neurology. 2015;53(4):293-300.
99. Wadman R, Wijngaarde C, Stam M, Bartels B, Otto L, Lemmink H, et al. Muscle strength and motor function throughout life in a cross - sectional cohort of 180 patients with spinal muscular atrophy types 1c–4. European journal of neurology. 2018;25(3):512-8.
100. Finkel RS, McDermott MP, Kaufmann P, Darras BT, Chung WK, Sproule DM, et al. Observational study of spinal muscular atrophy type I and implications for clinical trials. Neurology. 2014;83(9):810-7.
101. Kolb SJ, Coffey CS, Yankey JW, Krosschell K, Arnold WD, Rutkove SB, et al. Natural history of infantile - onset spinal muscular atrophy. Annals of neurology. 2017;82(6):883-91.
102. Cances C, Vlodavets D, Comi GP, Masson R, Mazurkiewicz-Bełdzińska M, Saito K, et al. Natural history of Type 1 spinal muscular atrophy: a retrospective, global, multicenter study. Orphanet Journal of Rare Diseases. 2022;17(1):1-11.
103. Oskoui M, Levy G, Garland C, Gray J, O'hagen J, De Vivo D, et al. The changing natural history of spinal muscular atrophy type 1. Neurology. 2007;69(20):1931-6.
104. Zerres K, Rudnik-Schöneborn S, Forrest E, Lusakowska A, Borkowska J, Hausmanowa-Petrusewicz I. A collaborative study on the natural history of

childhood and juvenile onset proximal spinal muscular atrophy (type II and III SMA): 569 patients. Journal of the neurological sciences. 1997;146(1):67-72.
105. Annoussamy M, Seferian AM, Daron A, Péréon Y, Cances C, Vuillerot C, et al. Natural history of Type 2 and 3 spinal muscular atrophy: 2 - year NatHis - SMA study. Annals of Clinical and Translational Neurology. 2021;8(2):359-73.
106. Kaufmann P, McDermott MP, Darras BT, Finkel RS, Sproule DM, Kang PB, et al. Prospective cohort study of spinal muscular atrophy types 2 and 3. Neurology. 2012;79(18):1889-97.
107. Lusakowska A, Jedrzejowska M, Kaminska A, Janiszewska K, Grochowski P, Zimowski J, et al. Observation of the natural course of type 3 spinal muscular atrophy: data from the polish registry of spinal muscular atrophy. Orphanet Journal of Rare Diseases. 2021;16:1-9.
108. Piepers S, Van Den Berg L, Brugman F, Scheffer H, Ruiterkamp-Versteeg M, Van Engelen B, et al. A natural history study of late onset spinal muscular atrophy types 3b and 4. Journal of neurology. 2008;255:1400-4.
109. Wijngaarde CA, Brink RC, de Kort FA, Stam M, Otto LA, Asselman F-L, et al. Natural course of scoliosis and lifetime risk of scoliosis surgery in spinal muscular atrophy. Neurology. 2019;93(2):e149-e58.
110. Peña-Longobardo LM, Aranda-Reneo I, Oliva-Moreno J, Litzkendorf S, Durand-Zaleski I, Tizzano E, et al. The economic impact and health-related quality of life of spinal muscular atrophy. An analysis across Europe. International Journal of Environmental Research and Public Health. 2020;17(16):5640.
111. López-Bastida J, Peña-Longobardo LM, Aranda-Reneo I, Tizzano E, Sefton M, Oliva-Moreno J. Social/economic costs and health-related quality of life in patients with spinal muscular atrophy (SMA) in Spain. Orphanet Journal of Rare Diseases. 2017;12(1):1-7.
112. Paracha N, Hudson P, Mitchell S, Sutherland CS. Systematic literature review to assess economic evaluations in spinal muscular atrophy (SMA). Pharmacoeconomics. 2021:1-21.
113. Marcellusi A, Bini C, Casiraghi J, D'Ambrosio F, Rotundo MA, Pallara A, et al. Cost of illness of spinal muscular atrophy (SMA) in Italy. Global & Regional Health Technology Assessment. 2019;2019:2284240319867662.
114. Paracha N, Hudson P, Mitchell S, Sutherland CS. Systematic Literature Review to Assess the Cost and Resource Use Associated with Spinal Muscular Atrophy Management. PharmacoEconomics. 2022;40(1):11-38.
115. Josep D, Alicia M. Patient characteristics and hospitalisation costs of spinal muscular atrophy in Spain: a retrospective multicentre database analysis. BMJ Open. 2019;9(11):e031271.
116. Tan H, Gu T, Chen E, Punekar R, Shieh PB. Healthcare Utilization, Costs of Care, and Mortality Among Psatients With Spinal Muscular Atrophy. Journal of health economics and outcomes research. 2019;6(3):185-95.
117. Ali I, Gilchrist FJ, Carroll WD, Alexander J, Clayton S, Kulshrestha R, et al. Healthcare utilisation in children with SMA type 1 treated with nusinersen: a single centre retrospective review. BMJ paediatrics open. 2019;3(1):e000572.
118. Droege M, Sproule D, Arjunji R, Gauthier-Loiselle M, Cloutier M, Dabbous O. Economic burden of spinal muscular atrophy in the United States: a contemporary assessment. Journal of medical economics. 2020;23(1):70-9.

119. Jedrzejowska M, Milewski M, Zimowski J, Zagozdzon P, Kostera-Pruszczyk A, Borkowska J, et al. Incidence of spinal muscular atrophy in Poland–more frequent than predicted? Neuroepidemiology. 2010;34(3):152-7.
120. Ogino S, Wilson RB, Gold B. New insights on the evolution of the SMN1 and SMN2 region: simulation and meta-analysis for allele and haplotype frequency calculations. European journal of human genetics. 2004;12(12):1015-23.
121. Lazarin GA, Haque IS, Nazareth S, Iori K, Patterson AS, Jacobson JL, et al. An empirical estimate of carrier frequencies for 400+ causal Mendelian variants: results from an ethnically diverse clinical sample of 23,453 individuals. Genetics in Medicine. 2013;15(3):178-86.
122. Wilson RB, Ogino S. Carrier frequency of spinal muscular atrophy. The Lancet. 2008;372(9649):1542.
123. Saffari A, Kölker S, Hoffmann GF, Weiler M, Ziegler A. Novel challenges in spinal muscular atrophy–How to screen and whom to treat? Annals of clinical and translational neurology. 2019;6(1):197-205.
124. World Health Organization. Screening programmes: A short guide [Internet]. Copenhagan: World Health Organization; 2020 [cited 2023 March 23]. Available from: https://apps.who.int/iris/bitstream/handle/10665/330829/9789289054782-eng.pdf?sequence=1&isAllowed=y.
125. 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(7):e1000097.
126. Abiusi E, Vaisfeld A, Fiori S, Novelli A, Spartano S, Faggiano MV, et al. Experience of a 2-year spinal muscular atrophy NBS pilot study in Italy: towards specific guidelines and standard operating procedures for the molecular diagnosis. Journal of Medical Genetics. 2022.
127. Baker MW, Mochal ST, Dawe SJ, Wiberley-Bradford AE, Cogley MF, Zeitler BR, et al. Newborn screening for spinal muscular atrophy: the Wisconsin first year experience. Neuromuscular Disorders. 2022;32(2):135-41.
128. Boemer F, Caberg J, Dideberg V, Beckers P, Marie S, Marcelis L, et al. (S) un (M) ay (A) rise on SMA: the hope of a region without spinal muscular atrophy. Revue medicale de Liege. 2019;74(9).
129. Boemer F, Caberg J-H, Dideberg V, Dardenne D, Bours V, Hiligsmann M, et al. Newborn screening for SMA in Southern Belgium. Neuromuscular Disorders. 2019;29(5):343-9.
130. Chan SH-S, Chae J-H, Chien Y-H, Ko T-S, Lee JH, Lee YJ, et al. Nusinersen in spinal muscular atrophy type 1 from neonates to young adult: 1-year data from three Asia-Pacific regions. Journal of Neurology, Neurosurgery & Psychiatry. 2021;92(11):1244-6.
131. Chien Y-H, Chiang S-C, Weng W-C, Lee N-C, Lin C-J, Hsieh W-S, et al. Presymptomatic diagnosis of spinal muscular atrophy through newborn screening. The Journal of pediatrics. 2017;190:124-9. e1.
132. Czibere L, Burggraf S, Fleige T, Glück B, Keitel LM, Landt O, et al. High-throughput genetic newborn screening for spinal muscular atrophy by rapid nucleic acid extraction from dried blood spots and 384-well qPCR. European Journal of Human Genetics. 2020;28(1):23-30.

133. Dangouloff T, Hiligsmann M, Deconinck N, D'Amico A, Seferian AM, Boemer F, et al. Financial cost and quality of life of patients with spinal muscular atrophy identified by symptoms or newborn screening. Developmental Medicine & Child Neurology. 2023;65(1):67-77.
134. Elkins K, Wittenauer A, Hagar AF, Logan R, Sekul E, Xiang Y, et al. Georgia state spinal muscular atrophy newborn screening experience: Screening assay performance and early clinical outcomes. American Journal of Medical Genetics Part C: Seminars in Medical Genetics. 2022;190(2):187-96.
135. Hale JE, Darras BT, Swoboda KJ, Estrella E, Chen JYH, Abbott M-A, et al. Massachusetts' findings from statewide newborn screening for spinal muscular atrophy. International Journal of Neonatal Screening. 2021;7(2):26.
136. Kariyawasam D, Russell JS, Wiley V, Alexander IE, Farrar MA. The implementation of newborn screening for spinal muscular atrophy: the Australian experience. Genetics in Medicine. 2020;22(3):557-65.
137. Kariyawasam DS, D'Silva AM, Sampaio H, Briggs N, Herbert K, Wiley V, et al. Newborn screening for spinal muscular atrophy in Australia: a non-randomised cohort study. The Lancet Child & Adolescent Health. 2023.
138. Kay DM, Stevens CF, Parker A, Saavedra-Matiz CA, Sack V, Chung WK, et al. Implementation of population-based newborn screening reveals low incidence of spinal muscular atrophy. Genetics in Medicine. 2020;22(8):1296-302.
139. Kernohan KD, McMillan HJ, Yeh E, Lacaria M, Kowalski M, Campbell C, et al. Ontario Newborn Screening for Spinal Muscular Atrophy: The First Year. Canadian Journal of Neurological Sciences. 2022;49(6):821-3.
140. Kölbel H, Vill K, Schwartz O, Blaschek A, Nennstiel U, Schara-Schmidt U, et al. Neugeborenenscreeningprogramm für die spinale Muskelatrophie. Der Nervenarzt. 2022;93(2).
141. Kraszewski JN, Kay DM, Stevens CF, Koval C, Haser B, Ortiz V, et al. Pilot study of population-based newborn screening for spinal muscular atrophy in New York state. Genetics in Medicine. 2018;20(6):608-13.
142. Kucera KS, Taylor JL, Robles VR, Clinard K, Migliore B, Boyea BL, et al. A voluntary statewide newborn screening pilot for spinal muscular atrophy: results from early check. International Journal of Neonatal Screening. 2021;7(1):20.
143. Lee BH, Deng S, Chiriboga CA, Kay DM, Irumudomon O, Laureta E, et al. Newborn Screening for spinal muscular atrophy in New York State: clinical outcomes from the first 3 years. Neurology. 2022;99(14):e1527-e37.
144. Lin Y, Lin C-H, Yin X, Zhu L, Yang J, Shen Y, et al. Newborn screening for spinal muscular atrophy in China using DNA mass spectrometry. Frontiers in genetics. 2019;10:1255.
145. Matteson J, Wu CH, Mathur D, Tang H, Sciortino S, Feuchtbaum L, et al. California's experience with SMA newborn screening: A successful path to early intervention. Journal of Neuromuscular Diseases. 2022(Preprint):1-9.
146. Müller-Felber W, Vill K, Schwartz O, Gläser D, Nennstiel U, Wirth B, et al. Infants diagnosed with spinal muscular atrophy and 4 SMN2 copies through newborn screening–opportunity or burden? Journal of neuromuscular diseases. 2020;7(2):109-17.

147. Noguchi Y, Bo R, Nishio H, Matsumoto H, Matsui K, Yano Y, et al. PCR-based screening of spinal muscular atrophy for newborn infants in hyogo prefecture, Japan. Genes. 2022;13(11):2110.
148. Sawada T, Kido J, Sugawara K, Yoshida S, Ozasa S, Nomura K, et al. Newborn screening for spinal muscular atrophy in Japan: One year of experience. Molecular Genetics and Metabolism Reports. 2022;32:100908.
149. Schwartz O, Kölbel H, Blaschek A, Gläser D, Burggraf S, Röschinger W, et al. Spinal Muscular Atrophy–Is Newborn Screening Too Late for Children with Two SMN2 Copies? Journal of Neuromuscular Diseases. 2022(Preprint):1-8.
150. Vill K, Kölbel H, Schwartz O, Blaschek A, Olgemöller B, Harms E, et al. One year of newborn screening for SMA–Results of a German pilot project. Journal of neuromuscular diseases. 2019;6(4):503-15.
151. Vill K, Schwartz O, Blaschek A, Gläser D, Nennstiel U, Wirth B, et al. Newborn screening for spinal muscular atrophy in Germany: clinical results after 2 years. Orphanet journal of rare diseases. 2021;16:1-10.
152. Weng W-C, Hsu Y-K, Chang F-M, Lin C-Y, Hwu W-L, Lee W-T, et al. CMAP changes upon symptom onset and during treatment in spinal muscular atrophy patients: lessons learned from newborn screening. Genetics in Medicine. 2021;23(2):415-20.
153. Kariyawasam DS, D'Silva AM, Sampaio H, Briggs N, Herbert K, Wiley V, et al. Newborn screening for spinal muscular atrophy in Australia: a non-randomised cohort study. Lancet Child Adolesc Health. 2023.
154. Dangouloff T, Hiligsmann M, Deconinck N, D'Amico A, Seferian AM, Boemer F, et al. Financial cost and quality of life of patients with spinal muscular atrophy identified by symptoms or newborn screening. Dev Med Child Neurol. 2023;65(1):67-77.
155. Kariyawasam DS, D'Silva AM, Vetsch J, Wakefield CE, Wiley V, Farrar MA. "We needed this": perspectives of parents and healthcare professionals involved in a pilot newborn screening program for spinal muscular atrophy. EClinicalMedicine. 2021;33:100742.
156. Kernohan KD, Chakraborty P. Additional cases of SMA detected through Ontario newborn screening: Personal communication with HIQA. 2023.
157. Health Information and Quality Authority. Review of processes in use to inform the expansion of newborn bloodspot screening programmes [Internet]. Dublin: Health Information and Quality Authority; 2021 [cited 2023 August 24]. Available from: https://www.hiqa.ie/areas-we-work/health-technology-assessment.
158. National Health Service (NHS). Guidelines for newborn blood spot sampling [Internet]. London: Public Health England; 2016 [cited 2023 August 24]. Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/899485/Guidelines_for_Newborn_Blood_Spot_Sampling_March_2016.pdf.
159. Romanelli Tavares VL, Monfardini F, Lourenço NCV, da Rocha KM, Weinmann K, Pavanello R, et al. Newborn screening for 5q spinal muscular atrophy: comparisons between real-time PCR methodologies and cost estimations for future implementation programs. International Journal of Neonatal Screening. 2021;7(3):53.

160. Pyatt RE, Prior TW. A feasibility study for the newborn screening of spinal muscular atrophy. Genetics in Medicine. 2006;8(7):428-37.
161. Taylor JL, Lee FK, Yazdanpanah GK, Staropoli JF, Liu M, Carulli JP, et al. Newborn blood spot screening test using multiplexed real-time PCR to simultaneously screen for spinal muscular atrophy and severe combined immunodeficiency. Clinical chemistry. 2015;61(2):412-9.
162. Vorster E, Essop FB, Rodda JL, Krause A. Spinal muscular atrophy in the Black South African population: a matter of rearrangement? Frontiers in Genetics. 2020;11:54.
163. Aragon-Gawinska K, Mouraux C, Dangouloff T, Servais L. Spinal Muscular Atrophy Treatment in Patients Identified by Newborn Screening—A Systematic Review. Genes. 2023;14(7):1377.
164. Butterfield RJ, editor Spinal muscular atrophy treatments, newborn screening, and the creation of a neurogenetics urgency. Seminars in pediatric neurology; 2021: Elsevier.
165. Blaschek A, Kölbel H, Schwartz O, Köhler C, Gläser D, Eggermann K, et al. Newborn Screening for SMA–Can a Wait-and-See Strategy be Responsibly Justified in Patients With Four SMN2 Copies? Journal of Neuromuscular Diseases. 2022(Preprint):1-9.
166. HSE Medicines Management Programme. Managed Access Protocols for SMN Dependent Drugs: Personal communication with HIQA. 2023.
167. HSE Corporate Pharmaceutical Unit. Reimbursement status of drugs to treat SMA: Personal communication with HIQA. 2023.
168. European Medicines Agency. European public assessment reports: background and context [Internet]. Amsterdam: European Medicines Agency; 2023 [cited 2023 July 24]. Available from: https://www.ema.europa.eu/en/medicines/what-we-publish-when/european-public-assessment-reports-background-context
169. Erdos J, Wild C. Mid- and long-term (at least 12 months) follow-up of patients with spinal muscular atrophy (SMA) treated with nusinersen, onasemnogene abeparvovec, risdiplam or combination therapies: A systematic review of real-world study data. Eur J Paediatr Neurol. 2022;39:1-10.
170. European Commission. Union Register of medicinal products [Internet]. Brussels: European Commission; 2023 [cited 2023 August 30]. Available from: https://ec.europa.eu/health/documents/community-register/html/h1531.htm.
171. National Centre for Pharmacoeconomics. Guidelines for Inclusion of Drug Costs in Pharmacoeconomic Evaluations (v3.2) [Internet]. Dublin: National Centre for Pharmacoeoeconomics,; 2023 [cited 2023 May 24]. Available from: https://www.ncpe.ie/wp-content/uploads/2022/01/Guidelines-for-Inclusion-of-Drug-Costs-in-Pharmacoeconomic-Evaluations-v3.1.pdf
172. HSE Corporate Pharmaceutical Unit. Price Realignment File for Implementation on 1 March 2023 [Internet]. Dublin: Health Services Executive; 2023 [cited 2023 March 24]. Available from: https://www.hse.ie/eng/about/who/cpu/ipha-price-reduction-2023/
173. Medicines Management Programme. Managed Access Protocol – Risdiplam (Evrysdi®) for the treatment of 5q Spinal Muscular Atrophy [Internet]. Dublin: HSE; 2023 [cited 2023 September 4]. Available from: https://www.hse.ie/eng/about/who/cspd/medicines-management/managed-

access-protocols/risdiplam-evrysdi/risdiplam-evrysdi-managed-access-protocol.pdf.
174. Medicines Management Programme. Managed Access Protocol – Nusinersen (SPINRAZA®) for the treatment of 5q Spinal Muscular Atrophy [Internet]. Dublin: HSE; 2022 [cited 2023 September 4]. Available from: https://www.hse.ie/eng/about/who/cspd/ncps/medicines-management/managed-access-protocols/nusinersen-spinraza-map-.pdf.
175. Medicines Management Programme. Managed Access Protocol – Onasemnogene abeparvovec (Zolgensma®) for the treatment of: 🕐 5q Spinal Muscular Atrophy (SMA) with a bi-allelic mutation in the SMN1 gene and a clinical diagnosis of SMA type 1, or pre-symptomatic patients with 5q SMA with a bi-allelic mutation in the SMN1 gene and up to 3 copies of the SMN2 gene [Internet]. Dublin: HSE; 2021 [cited 2023 September 4]. Available from: https://www.hse.ie/eng/about/who/cspd/ncps/medicines-management/managed-access-protocols/onasemnogene-abeparvovec-zolgensma/onasemnogene-abeparvovec-zolgensma.pdf.
176. National Centre for Pharmacoeconomics. Budget impact model template (v1.8) [Internet]. Dublin: National Centre for Pharmacoeconomics; 2023 [cited 2023 July 24]. Available from: https://www.ncpe.ie/submission-process/submission-templates/budget-impact-model-template/
177. Ramdas S, Servais L. New treatments in spinal muscular atrophy: an overview of currently available data. Expert Opin Pharmacother. 2020;21(3):307-15.
178. Messina S, Sframeli M. New Treatments in Spinal Muscular Atrophy: Positive Results and New Challenges. J Clin Med. 2020;9(7).
179. Kakazu J, Walker NL, Babin KC, Trettin KA, Lee C, Sutker PB, et al. Risdiplam for the Use of Spinal Muscular Atrophy. Orthop Rev (Pavia). 2021;13(2):25579.
180. European Medicines Agency. Evrysdi (risdiplam) [Internet]. Amsterdam: European Medicines Agency; 2023 [cited 2023 August 24]. Available from: https://www.ema.europa.eu/en/medicines/human/summaries-opinion/evrysdi-0
181. National Centre for Pharmacoeconomics. Nusinersin (Spinraza®) [Internet]. Dublin: National Centre for Pharmacoeconomics; 2017 [cited 2023 February 24]. Available from: https://www.ncpe.ie/nusinersin-spinraza/
182. National Centre for Pharmacoeconomics. Onasemnogene abeparvovec (Zolgensma®). HTA ID: 20021 [Internet]. Dublin: National Centre for Pharmacoeconomics,; 2021 [cited 2023 March 24]. Available from: https://www.ncpe.ie/onasemnogene-abeparvovec-zolgensma-hta-id-20021/
183. National Centre for Pharmacoeconomics. Risdiplam (Evrysdi™). HTA ID: 21006 [Internet]. Dublin: National Centre for Pharmacoeconomics; 2022 [cited 2023 March 24]. Available from: https://www.ncpe.ie/risdiplam-evrysdi-hta-id-21006/
184. HSE Corporate Pharmaceutical Unit. HSE Drugs Group - February 2023 Minutes [Internet]. Dublin: HSE; 2023 [cited 2023 July 21]. Available from: https://www.hse.ie/eng/about/who/cpu/drugs-group-minutes/hse-drugs-group-minutes-february-2023.pdf
185. HSE Corporate Pharmaceutical Unit. HSE Drugs Group - April 2023 Minutes [Internet]. Dublin: HSE; 2023 [cited 2023 July 21]. Available from:

https://www.hse.ie/eng/about/who/cpu/drugs-group-minutes/hse-drugs-group-minutes-april-2023.pdf
186. HSE Medicines Management Programme. Reimbursement status of drugs to treat SMA: Personal communication with HIQA. 2023.
187. De Vivo DC, Bertini E, Swoboda KJ, Hwu WL, Crawford TO, Finkel RS, et al. Nusinersen initiated in infants during the presymptomatic stage of spinal muscular atrophy: Interim efficacy and safety results from the Phase 2 NURTURE study. Neuromuscul Disord. 2019;29(11):842-56.
188. Strauss KA, Farrar MA, Muntoni F, Saito K, Mendell JR, Servais L, et al. Onasemnogene abeparvovec for presymptomatic infants with two copies of SMN2 at risk for spinal muscular atrophy type 1: the Phase III SPR1NT trial. Nat Med. 2022;28(7):1381-9.
189. Strauss KA, Farrar MA, Muntoni F, Saito K, Mendell JR, Servais L, et al. Onasemnogene abeparvovec for presymptomatic infants with three copies of SMN2 at risk for spinal muscular atrophy: the Phase III SPR1NT trial. Nat Med. 2022;28(7):1390-7.
190. clinicaltrials.gov. A Study of Risdiplam in Infants With Genetically Diagnosed and Presymptomatic Spinal Muscular Atrophy (Rainbowfish) [Internet]. Bethesda: U.S. National National Library of Medicine; 2018 [updated 2022 December 21; cited 2023 January 27]. Available from: https://clinicaltrials.gov/ct2/show/NCT03779334.
191. Finkel RS, Mercuri E, Darras BT, Connolly AM, Kuntz NL, Kirschner J, et al. Nusinersen versus Sham Control in Infantile-Onset Spinal Muscular Atrophy. N Engl J Med. 2017;377(18):1723-32.
192. Mercuri E, Darras BT, Chiriboga CA, Day JW, Campbell C, Connolly AM, et al. Nusinersen versus Sham Control in Later-Onset Spinal Muscular Atrophy. N Engl J Med. 2018;378(7):625-35.
193. Day JW, Finkel RS, Chiriboga CA, Connolly AM, Crawford TO, Darras BT, et al. Onasemnogene abeparvovec gene therapy for symptomatic infantile-onset spinal muscular atrophy in patients with two copies of SMN2 (STR1VE): an open-label, single-arm, multicentre, phase 3 trial. Lancet Neurol. 2021;20(4):284-93.
194. clinicaltrials.gov. Investigate Safety, Tolerability, PK, PD and Efficacy of Risdiplam (RO7034067) in Infants With Type1 Spinal Muscular Atrophy (FIREFISH) [Internet]. Bethesda: U.S. National National Library of Medicine; 2016 [updated 2023 January 20; cited 2023 January 27]. Available from: https://clinicaltrials.gov/ct2/show/NCT02913482.
195. Baranello G, Darras BT, Day JW, Deconinck N, Klein A, Masson R, et al. Risdiplam in Type 1 Spinal Muscular Atrophy. N Engl J Med. 2021;384(10):915-23.
196. Mercuri E, Deconinck N, Mazzone ES, Nascimento A, Oskoui M, Saito K, et al. Safety and efficacy of once-daily risdiplam in type 2 and non-ambulant type 3 spinal muscular atrophy (SUNFISH part 2): a phase 3, double-blind, randomised, placebo-controlled trial. Lancet Neurol. 2022;21(1):42-52.
197. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ (Clinical research ed). 2021;372:n71.

198. Health Information and Quality Authority. Protocol for the Health Technology Assessment of the addition of spinal muscular atrophy (SMA) to the National Newborn Bloodspot Screening Programme [Internet]. Dublin: Health Information and Quality Authority; 2023 [updated 2023 July 20; cited 2023 July 31]. Available from: https://www.hiqa.ie/reports-and-publications/health-technology-assessment/protocol-health-technology-assessment
199. 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(4):463-72.
200. Health Information and Quality Authority. Guidelines for the Economic Evaluation of Health Technologies in Ireland 2020 [Internet]. Dublin: Health Information and Quality Authority; 2020 [cited 2023 February 16]. Available from: https://www.hiqa.ie/reports-and-publications/health-technology-assessment/guidelines-economic-evaluation-health.
201. Woods B, Revill P, Sculpher M, Claxton K. Country-Level Cost-Effectiveness Thresholds: Initial Estimates and the Need for Further Research. Value Health. 2016;19(8):929-35.
202. Iino H, Hashiguchi M, Hori S. Estimating the range of incremental cost-effectiveness thresholds for healthcare based on willingness to pay and GDP per capita: A systematic review. PLOS ONE. 2022;17(4):e0266934.
203. 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(2):240-5.
204. 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(2):174-82.
205. Velikanova R, van der Schans S, Bischof M, van Olden RW, Postma M, Boersma C. Cost-Effectiveness of Newborn Screening for Spinal Muscular Atrophy in The Netherlands. Value Health. 2022;25(10):1696-704.
206. Weidlich D, Servais L, Kausar I, Howells R, Bischof M. Cost-Effectiveness of Newborn Screening for Spinal Muscular Atrophy in England. Neurology and therapy. 2023;12(4):1205-20.
207. Shih ST, Farrar MA, Wiley V, Chambers G. Newborn screening for spinal muscular atrophy with disease-modifying therapies: a cost-effectiveness analysis. J Neurol Neurosurg Psychiatry. 2021;92(12):1296-304.
208. Jalali A, Rothwell E, Botkin JR, Anderson RA, Butterfield RJ, Nelson RE. Cost-Effectiveness of Nusinersen and Universal Newborn Screening for Spinal Muscular Atrophy. J Pediatr. 2020;227:274-80 e2.
209. Shih STF, Keller E, Wiley V, Farrar MA, Wong M, Chambers GM. Modelling the Cost-Effectiveness and Budget Impact of a Newborn Screening Program for Spinal Muscular Atrophy and Severe Combined Immunodeficiency. Int J Neonatal Screen. 2022;8(3).
210. Finkel RS, Farrar MA, Vlodavets D, Servais L, Zanoteli E, Al-Muhaizea M, et al. RAINBOWFISH: Preliminary Efficacy and Safety Data in Risdiplam-Treated

Infants with Presymptomatic SMA (P17-5.003). Neurology. 2022;98(18 Supplement):1636.
211. Mendell JR, Al-Zaidy SA, Lehman KJ, McColly M, Lowes LP, Alfano LN, et al. Five-Year Extension Results of the Phase 1 START Trial of Onasemnogene Abeparvovec in Spinal Muscular Atrophy. JAMA neurology. 2021;78(7):834-41.
212. Cordts I, Lingor P, Friedrich B, Pernpeintner V, Zimmer C, Deschauer M, et al. Intrathecal nusinersen administration in adult spinal muscular atrophy patients with complex spinal anatomy. Therapeutic advances in neurological disorders. 2020;13:1756286419887616.
213. Sutherland CS, Hudson P, Mitchell S, Paracha N. Systematic Literature Review to Identify Utility Values in Patients with Spinal Muscular Atrophy (SMA) and Their Caregivers. PharmacoEconomics. 2022;40(1):39-67.
214. Khanna D, Khadka J, Mpundu-Kaambwa C, Lay K, Russo R, Ratcliffe J, et al. Are We Agreed? Self- Versus Proxy-Reporting of Paediatric Health-Related Quality of Life (HRQoL) Using Generic Preference-Based Measures: A Systematic Review and Meta-Analysis. PharmacoEconomics. 2022;40(11):1043-67.
215. National Institute for Health and Care Excellence. Onasemnogene abeparvovec for treating spinal muscular atrophy [Internet]. London: National Institute for Health and Care Excellence; 2021 [cited 2023 February 22]. Available from: https://www.nice.org.uk/guidance/hst15
216. Paracha N, Hudson P, Mitchell S, Sutherland CS. Systematic Literature Review to Assess Economic Evaluations in Spinal Muscular Atrophy (SMA). Pharmacoeconomics. 2022;40(Suppl 1):69-89.
217. Dangouloff T, Botty C, Beaudart C, Servais L, Hiligsmann M. Systematic literature review of the economic burden of spinal muscular atrophy and economic evaluations of treatments. Orphanet J Rare Dis. 2021;16(1):47.
218. Lundh A, Lexchin J, Mintzes B, Schroll JB, Bero L. Industry sponsorship and research outcome. Cochrane database of systematic reviews. 2017(2).
219. UK National Screening Committee. Progress and next steps in the UK NSC assessment of newborn screening for SMA [Internet]. 2023 [updated 2023 August 4; cited 2023 August 11]. Available from: https://nationalscreening.blog.gov.uk/2023/08/04/progress-and-next-steps-in-the-uk-nsc-assessment-of-newborn-screening-for-sma/
220. Philips Z, Ginnelly L, Sculpher M, Claxton K, Golder S, Riemsma R, et al. Review of guidelines for good practice in decision-analytic modelling in health technology assessment. Health technology assessment (Winchester, England). 2004;8(36):iii-iv, ix-xi, 1-158.
221. Wijnen B, Van Mastrigt G, Redekop WK, Majoie H, De Kinderen R, Evers S. How to prepare a systematic review of economic evaluations for informing evidence-based healthcare decisions: data extraction, risk of bias, and transferability (part 3/3). Expert review of pharmacoeconomics & outcomes research. 2016;16(6):723-32.
222. Scherer RW, Saldanha IJ. How should systematic reviewers handle conference abstracts? A view from the trenches. Systematic Reviews. 2019;8(1):264.
223. Department of Health. Minister for Health approves 10th condition for the National Newborn Bloodspot Screening Programme [Internet]. 2023 [updated

2023 January 25; cited 2023 July 03]. Available from: https://www.gov.ie/en/press-release/8e592-minister-for-health-approves-10th-condition-for-the-national-newborn-bloodspot-screening-programme/.
224. European Network for Health Technology Assessment (EUnetHTA). HTA Core Model [Internet]. European Network for Health Technology Assessment (EUnetHTA),; [cited 2023 March 22]. Available from: https://www.eunethta.eu/hta-core-model/.
225. Shabani M, Borry P. Rules for processing genetic data for research purposes in view of the new EU General Data Protection Regulation. European Journal of Human Genetics. 2018;26(2):149-56.
226. Royal College of Physicians and Royal College of Pathologists and British Society for Genetic Medicine. Consent and confidentiality in genomic medicine: Guidance on the use of genetic and genomic information in the clinic. 3rd edition. Report of the Joint Committee on Genomics in Medicine. [Internet]. London: Royal College of Physicians; 2019 [cited 2023 August 03]. Available from: https://www.rcplondon.ac.uk/projects/outputs/consent-and-confidentiality-genomic-medicine.
227. General Data Protection Regulation. Recital 34: Genetic Data [Internet]. Intersoft Consulting; [cited 2023 August 02]. Available from: https://gdpr-info.eu/recitals/no-34/.
228. Vidal-Folch N, Gavrilov D, Raymond K, Rinaldo P, Tortorelli S, Matern D, et al. Multiplex droplet digital PCR method applicable to newborn screening, carrier status, and assessment of spinal muscular atrophy. Clinical chemistry. 2018;64(12):1753-61.
229. Wilson JMG, Jungner G, Organization WH. Principles and practice of screening for disease [Internet]. Geneva: World Health Organization; 1968 [cited 2023 July 31]. Available from: https://iris.who.int/bitstream/handle/10665/37650/WHO_PHP_34.pdf?sequence=17&isAllowed=y.
230. World Health Organisation. Screening programmes: a short guide: 2020 [Available from: https://apps.who.int/iris/bitstream/handle/10665/330829/9789289054782-eng.pdf.
231. National Screening Advisory Committee. Criteria for Appraising the Viability, Effectiveness and Appropriateness of a Screening Programme [Internet]. Dublin: Department of Health; 2020 [cited 2023 August 24]. Available from: https://assets.gov.ie/94190/0461e253-5a2f-42c5-976d-ce9cf6d8f312.pdf.
232. Health Service Executive. What you need to know about heel prick testing [Internet]. Dublin HSE; 2022 [updated 2022 May; cited 2022 December 15]. Available from: https://www2.hse.ie/file-library/heel-prick-screening/what-you-need-to-know-about-heel-prick-screening.pdf.
233. Boardman FK, Sadler C, Young PJ. Newborn genetic screening for spinal muscular atrophy in the UK: The views of the general population. Molecular genetics & genomic medicine. 2018;6(1):99-108.
234. National Newborn Bloodspot Screening Laboratory. A Practical Guide to Newborn Bloodspot Screening In Ireland 9th Edition [Internet]. Dublin: Health Service Executive,; 2022 [cited 2023 August 23]. Available from: https://www.hse.ie/eng/health/child/newbornscreening/newbornbloodspotscr

eening/information-for-professionals/a-practical-guide-to-newborn-bloodspot-screening-in-ireland.pdf.
235. Health Information and Quality Authority. Guidelines for Budget Impact Analysis [Internet]. Dublin: Health Information and Quality Authority; 2018 [cited 2023 May 26]. Available from: https://www.hiqa.ie/reports-and-publications/health-technology-assessment/guidelines-budget-impact-analysis-health.
236. Central Statistics Office. PEB08 - Projected Annual Births, Deaths, Internal Migration and International Migration [Internet]. Cork: Central Statistics Office; [updated 2021 March 15; cited 2023 August 24]. Available from: https://data.cso.ie/table/PEB08.
237. Revenue. VAT rates database [Internet]. Dublin: Office of the Revenue Commissioners; 2023 [cited 2023 July 21]. Available from: https://www.revenue.ie/en/vat/vat-rates/search-vat-rates/vat-rates-database.aspx
238. Revenue. VAT rates. Maintenance - movable goods (certain repair and related services) [Internet]. Dublin: Office of the Revenue Commissioners; 2023 [cited 2023 July 27]. Available from: https://www.revenue.ie/en/vat/vat-rates/search-vat-rates/M/maintenance-movable-goods-certain-repair-and-related-services-.aspx
239. Department of Public Expenditure and Reform. Public procurement guidelines for goods and services. Version 2: Issued January 2019 [Internet]. Dublin: Department of Public Expenditure and Reform; 2019 [cited 2023 August 04]. Available from: https://assets.gov.ie/135773/d186ba93-dd70-45fe-83d3-8d9c3bb9d4a6.pdf
240. Healthcare Pricing Office. ABF 2023 Admitted Patient Price List [Internet]. Dublin: HSE; 2023 [cited 2023 July 12]. Available from: http://www.hpo.ie/abf/ABF2023AdmittedPatientPriceListv1.pdf
241. Health Service Executive. Consolidated salary scales in accordance with the FEMPI Acts, the Public Service Agreements and the Public Service Pay and Pensions Act 2017 [Internet]. 2023 [updated 2023 March 02; cited 2023 July 12]. Available from: https://www.hse.ie/eng/staff/resources/hr-circulars/final-1-march-2023-salary-scales.pdf
242. Healthcare Pricing Office. Personal communication with HIQA. 2023.
243. Revenue. VAT rates. Human medicine - Non-oral [Internet]. Dublin: Office of the Revenue Commissioners; 2023 [cited 2023 July 21]. Available from: https://www.revenue.ie/en/vat/vat-rates/search-vat-rates/H/human-medicine-non-oral.aspx.
244. Royal College of Paediatrics and Child Health. UK-WHO growth charts - 0-4 years [Internet]. London: Royal College of Paediatrics and Child Health; 2013 [updated 2013 January; cited 2023 July 03]. Available from: https://www.rcpch.ac.uk/resources/uk-who-growth-charts-0-4-years
245. Royal College of Paediatrics and Child Health. UK-WHO growth charts - 2-18 years: [Available from: https://www.rcpch.ac.uk/resources/uk-who-growth-charts-2-18-years Accessed 03/07/2023.
246. Revenue. VAT Rates. Human medicine - Oral (Medicine, medical equipment and appliances) [Internet]. 2023 [cited 2023 July 03]. Available from:

https://www.revenue.ie/en/vat/vat-rates/search-vat-rates/H/human-medicine-oral-medicine-medical-equipment-and-appliances.aspx

247. Houses of the Oireachtas. Dáil Éireann debate: Volume 1022 Number 6: Strike Action by the Medical Laboratory Scientists Association [Internet]. Dublin: Houses of the Oireachtas; 2022 [cited 2023 August 03]. Available from: https://www.oireachtas.ie/en/debates/debate/dail/2022-05-25/26/?highlight%5B0%5D=medical&highlight%5B1%5D=scientist&highlight%5B2%5D=currently.
248. Chan SHS, Wong CKH, Wu T, Wong W, Yu MKL, Au ICH, et al. Significant healthcare burden and life cost of spinal muscular atrophy: real-world data. The European Journal of Health Economics. 2022.
249. Chen G, Sharif B, Gerber B, Farris MS, Cowling T, Cabalteja C, et al. Epidemiology, healthcare resource utilization and healthcare costs for spinal muscular atrophy in Alberta, Canada. Journal of medical economics. 2021;24(sup1):51-9.
250. Darbà J. Management and current status of spinal muscular atrophy: a retrospective multicentre claims database analysis. Orphanet Journal of Rare Diseases. 2020;15(1):8.
251. Landfeldt E, Abner S, Pechmann A, Sejersen T, McMillan HJ, Lochmüller H, et al. Caregiver Burden of Spinal Muscular Atrophy: A Systematic Review. Pharmacoeconomics. 2023;41(3):275-93.
252. Leibrock B, Landfeldt E, Hussong J, Huelle T, Mattheus H, Thiele S, et al. Areas of improvement in the medical care of SMA: evidence from a nationwide patient registry in Germany. Orphanet Journal of Rare Diseases. 2023;18(1):32.
253. Beneluxa. Beneluxa Statement on high cost SMA treatments [Internet]. Beneluxa; 2021 [updated 2021 May 28; cited 2023 June 29]. Available from: https://beneluxa.org/archive#toc-28-may-2021-beneluxa-statement-on-high-cost-sma-treatments.
254. Zorginstituut Nederland. Sluice drug package advice onasemnogene abeparvovec (Zolgensma®) in the treatment of spinal muscular atrophy (SMA) [Internet]. Diemen: Zorginstituut Nederland; 2021 [cited 2023 June 29]. Available from: https://www.zorginstituutnederland.nl/publicaties/adviezen/2021/05/06/pakketadvies-sluisgeneesmiddel-onasemnogene-abeparvovec-zolgensma
255. National Institute for Health and Care Excellence. Using other disease-modifying medicines for spinal muscular strophy (MSA) after onamennogene abeparvovec treatment [Internet]. London: National Institute for Health and Care Excellence, ; 2021 [cited 2023 July 26]. Available from: https://www.nice.org.uk/guidance/ta755/resources/appendix-a-using-other-treatments-after-onasemnogene-pdf-10897406894
256. National Institute for Health and Care Excellence. Risdiplam for treating spinal muscular atrophy. Questions and answers on the managed access agreement for risdiplam (January 2022) [Internet]. London: National Institute for Health and Care Excellence; 2021 [updated 2021 December 16; cited 2023 July 26]. Available from: https://www.nice.org.uk/guidance/ta755/resources/questions-and-answers-on-the-managed-access-agreement-for-risdiplam-january-2022-10951526557

257. clinicaltrials.gov. A Study of Nusinersen Among Participants With Spinal Muscular Atrophy Who Received Onasemnogene Abeparvovec (RESPOND). ClinicalTrials.gov Identifier: NCT04488133 [Internet]. Bethesda: U.S. National Library of Medicine; 2020 [updated 2023 June 19; cited 2023 July 26]. Available from: https://classic.clinicaltrials.gov/ct2/show/NCT04488133.
258. Black N, Martineau F, Manacorda T. Diagnostic odyssey for rare diseases: exploration of potential indicators [Internet]. London: Policy Innovation Research Unit; 2015 [Available from: https://piru.ac.uk/assets/files/Rare%20diseases%20Final%20report.pdf.
259. Kölbel H, Modler L, Blaschek A, Schara-Schmidt U, Vill K, Schwartz O, et al. Parental Burden and Quality of Life in 5q-SMA Diagnosed by Newborn Screening. Children. 2022;9(12):1829.
260. Grob R. Qualitative research on expanded prenatal and newborn screening: robust but marginalized. Hastings Center Report. 2019;49:S72-S81.
261. Moody L, Choudhry K. Parental views on informed consent for expanded newborn screening. Health Expectations. 2013;16(3):239-50.
262. Boardman FK, Young PJ, Griffiths FE. Newborn screening for spinal muscular atrophy: The views of affected families and adults. American Journal of Medical Genetics Part A. 2017;173(6):1546-61.
263. Boardman FK, Young PJ, Griffiths FE. Impairment experiences, identity and attitudes towards genetic screening: The views of people with spinal muscular atrophy. Journal of Genetic Counseling. 2018;27(1):69-84.
264. Serra-Juhe C, Tizzano EF. Perspectives in genetic counseling for spinal muscular atrophy in the new therapeutic era: early pre-symptomatic intervention and test in minors. European Journal of Human Genetics. 2019;27(12):1774-82.
265. Borry P, Evers-Kiebooms G, Cornel MC, Clarke A, Dierickx K. Genetic testing in asymptomatic minors. European Journal of Human Genetics. 2009;17(6):711-9.
266. Ooi K. The pitfalls of overtreatment: Why more care is not necessarily beneficial. Asian Bioethics Review. 2020;12(4):399-417.
267. Newson AJ, Dive L, Cini J, Hurley E, Farrar MA. Ethical aspects of the changing landscape for spinal muscular atrophy management in Australia. Australian journal of general practice. 2022;51(3):131-5.
268. Rijksinstituut voor Volksgezondheid en Milieu. Execution test addition Spinal Muscular Atrophy on the neonatal heel prick screening [Internet]. Bilthoven: Rijksinstituut voor Volksgezondheid en Milieu; 2020 [cited 2023 June 29]. Available from: https://www.rivm.nl/bibliotheek/rapporten/2020-0105.pdf
269. Rittenmeyer L, Huffman D, Alagna M, Moore E. The experience of adults who choose watchful waiting or active surveillance as an approach to medical treatment: a qualitative systematic review. JBI database of systematic reviews and implementation reports. 2016;14(2):174-255.
270. Sari DM, Wijaya LCG, Sitorus WDR, Dewi MM. Psychological burden in spinal muscular atrophy patients and their families: a systematic review. The Egyptian Journal of Neurology, Psychiatry and Neurosurgery. 2022;58(1):140.
271. Inhestern L, Brandt M, Driemeyer J, Denecke J, Johannsen J, Bergelt C. Experiences of Health Care and Psychosocial Needs in Parents of Children

with Spinal Muscular Atrophy. International Journal of Environmental Research and Public Health [Internet]. 2023; 20(7).
272. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Newborn screening for 5q-linked spinal muscular atrophy [Internet]. Cologne: Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen; 2020 [cited 2023 January 04]. Available from: https://www.iqwig.de/download/s18-02_newborn-screening-for-5q-linked-sma_extract-of-final-report_v1-0.pdf.
273. The Evidence-based Review Group. Evidence-based Review of Newborn Screening for Spinal Muscular Atrophy (SMA): Final Report 2018.
274. Costello Medical. Screening for spinal muscular atrophy External review against programme appraisal criteria for the UK National Screening Committee (UK NSC) [Internet]. London: UK National Screening Committee (Public Health England); 2018 [cited 2023 August 10]. Available from: https://www.google.com/url?sa=t&rct=j&q=&esrc=s&source=web&cd=&ved=2ahUKEwiT7qPbz8qBAxW1SkEAHcCIAp4QFnoECBkQAQ&url=https%3A%2F%2Fview-health-screening-recommendations.service.gov.uk%2Freview%2Fsma-2018%2Fdownload-documents%2Fcover_sheet%2F&usg=AOvVaw2Swf5VipRVqaBDh50sFQ2C&opi=89978449.
275. Health Resources and Services Administration. Review of Newborn Screening Implementation for Spinal Muscular Atrophy Final Report [Internet]. Maryland: Health Resources and Services Administration; 2020 [cited 2023 August 11]. Available from: https://www.hrsa.gov/sites/default/files/hrsa/advisory-committees/heritable-disorders/reports-recommendations/sma-nbs-implementation-report.pdf.
276. ClinicalTrials.gov. Newborn Screening for Spinal Muscular Atrophy (SMA-NBS) [Internet]. Bethesda: U.S. National National Library of Medicine; 2022 [updated 2022 August 1; cited 2023 August 11]. Available from: https://classic.clinicaltrials.gov/ct2/show/NCT05481164.
277. NHS England. NHS screening programmes: KPI reports 2021 to 2022 [Internet]. Redditch: NHS England; 2022 [updated 2023 March 23; cited 2023 August 11]. Available from: https://www.gov.uk/government/publications/nhs-screening-programmes-kpi-reports-2021-to-2022.
278. Harris R, Sawaya GF, Moyer VA, Calonge N. Reconsidering the criteria for evaluating proposed screening programs: reflections from 4 current and former members of the US Preventive Services Task Force. Epidemiologic reviews. 2011;33(1):20-35.
279. Bilinski A, Neumann P, Cohen J, Thorat T, McDaniel K, Salomon JA. When cost-effective interventions are unaffordable: Integrating cost-effectiveness and budget impact in priority setting for global health programs. PLoS Med. 2017;14(10):e1002397.
280. Food and Drug Administration. Evrysdi® (risdiplam) for oral solution :full prescribing information [Internet]. Maryland: Food and Drug Administration,; 2023 [cited 2023 April 19]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/213535s008lbl.pdf

281. Kariyawasam DST, Russell JS, Wiley V, Alexander IE, Farrar MA. The implementation of newborn screening for spinal muscular atrophy: the Australian experience. Genet Med. 2020;22(3):557-65.
282. Department of Education. Regional Projections of full-time enrolments. Primary and Second Level, 2021 - 2036 [Internet]. Dublin: Department of Education; 2021 [cited 2023 May 26]. Available from: https://assets.gov.ie/205796/e11837f2-b5f4-4786-9772-f8d5d98e7cfe.pdf.
283. Day JW, Finkel RS, Mercuri E, Swoboda KJ, Menier M, van Olden R, et al. Adeno-associated virus serotype 9 antibodies in patients screened for treatment with onasemnogene abeparvovec. Molecular therapy Methods & clinical development. 2021;21:76-82.

Appendices

Appendix Chapter 1

Table A1.1 NSAC criteria (for appraising the viability, effectiveness and appropriateness of a screening programme) by HTA domain [8]

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

Criterion No.	NSAC Grouping	Criterion	HTA domain(s)*
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 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.	Clinical effectiveness and safety, Ethical, social and legal issues
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

Criterion No.	NSAC Grouping	Criterion	HTA domain(s)*
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
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.

* 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). 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 Chapter 2

Table A2.1 Common functional outcome measures used in SMA

Outcome measure	Abbreviation	Description
Children Hospital of Philadelphia Infant Test of Neuromuscular Disorders	CHOP-INTEND	▪ Aims to evaluate the motor skills of patients with SMA type I and early childhood neuromuscular conditions ▪ Sixteen categories evaluated: spontaneous movement of upper extremity, spontaneous movement of lower extremity, hand grip, head in midline with visual stimulation, hip adductors, rolling elicited from legs, rolling elicited from arms, shoulder and elbow flexion and horizontal abduction, shoulder flexion and elbow flexion, knee extension, hip flexion and foot dorsiflexion, head control, elbow flexion, neck flexion, head and neck extension, and spinal curvation. ▪ Scoring is on a 0 to 4 scale for level of response (0 – no response, 1 – minimal, 2 – partial, 3 – nearly full, and 4 – complete). ▪ Maximum score of 64, with higher scores indicating better response.
Hammersmith Infant Neurological Examination	HINE	▪ Made of three parts examining neuromuscular function typically in those aged two to 24 months. ▪ Part 1: 26 different criteria based on movements, behaviour, cranial nerve function, protective reactions, reflexes and gross and fine motor function. Symmetry between left and right sides are also scored. Total scores can range from 0 to 78, with higher scores indicating better neurological function ▪ Part 2: assesses motor milestone achievements. There are eight categories assessed: voluntary grasp, kicking, head control, rolling, sitting, crawling, standing, and walking. Total scores can range from 0 to 26, with higher scores indicating better motor function

Outcome measure	Abbreviation	Description
		▪ Part 3: assesses behaviour. There are three categories assessed: state of consciousness, emotional state, and social orientation.
Hammersmith Function Motor Scale	HFMS	▪ Aims to evaluate neuromuscular function in those with type II and type III SMA, with some use in type I, typically in those aged over two years. ▪ Tests the child's ability to control the head, roll, achieve prop position, kneel, crawl, stand, and take at least 4 steps unaided. ▪ The maximum score is 40 with higher scores indicating higher function.
Hammersmith Function Motor Scale Expanded	HFMSE	▪ Expanded version of the HFMS including elements of GMFM with the goal of removing ceiling effect for type III SMA patients ▪ Made of 33 items assessing motor function. ▪ Maximum score of 66 with high scores indicating higher function
Revised Hammersmith Scale	RHS	▪ Modified version of HFMS for SMA incorporating additional elements such as WHO motor milestones assessment ▪ Milestones include: sitting without support, hands- and- knees crawling, standing with assistance, walking with assistance, standing alone, and walking alone. ▪ The test consists of 36 items, and the maximum score is 69 points with higher scores indicating higher function
WHO motor milestones	-	▪ Normative measure of developmental milestones ▪ Protocol includes six items: Sitting without support, Hands-and-knees crawling, Standing with assistance, Walking with assistance, "Standing alone, and Walking alone ▪ The standards are based on 'windows of achievement' rather than percentile with performance compared to established norms

Outcome measure	Abbreviation	Description
Revised Upper Limb Module	RULM	▪ Used to assess upper limb function in those with SMA aged over 30 months ▪ Items include putting a coin into a cup or elevating a cup to lips, picking a coin, bringing hand to shoulder, lifting weights, opening a zip lock, drawing a line on paper, and other tasks reflecting daily activities ▪ It contains 20 elements with a maximum score of 37 point
Gross Motor Function Measure	GMFM	▪ Assesses gross motor function in children aged over five years ▪ Consists of 88 items across five domains: lying and rolling, sitting, crawling and kneeling, standing, walking, running, and jumping ▪ Each scored from 0 to 3 with higher scores indicating higher gross motor function
Motor Function Measure-20	MFM-20	▪ Twenty item scale assessing motor function typically in those aged over two years ▪ Includes assessment of standing and transfers, axial and proximal motor function, distal motor function, and other functional levels (including the ability to walk). ▪ Maximum score of 60 with higher scores indicating higher function
Six minute walk test	6MWT	▪ Timed walking test typically used in those aged over four years who can ambulate ▪ The patient is asked to walk 25 metres on a flat surface for 6 minutes as many times as possible. ▪ Assessment considers: distance covered during the six minutes, distance covered during each minute of the test, time to complete each 25-metre walk, the number of falls, the difference between the distance walked in the first and last minute of the test

Outcome measure	Abbreviation	Description
		▪ Results are compared to those achieved by healthy participants matched according to gender, age, weight, and height.
Bayley Scales of Infant and Toddler Development	BSD-III	▪ Generic measure of development in infants and toddlers ▪ Includes five scales: cognitive, language, motor, social-emotional, and adaptive behaviour. ▪ Standardised mean motor score is 100 with lower scores reflective of impairment

A2.1 Surveillance recommendations for infants identified through newborn bloodspot screening for SMA in Ontario Canada

Table A2.2 Surveillance recommendations for children with two or three SMN2 copies

	Months of age													
Assessment	0	3	6	10	14	18	22	24	28	32	36	40	44	48
NMSK	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HINE	X		X	X	X	X	X	Stop when HFMSE initiated						
CHOP-INTEND			X	X	X	X	X	X	Continue if score < 50					
HFMSE					Start if CHOP-INTEND >= 50									
6MWT														X*
RULM														X*
CNDR enrolment	X													
Treatment initiation	X													

Key: 6MWT – 6 minute walk test; CHOP-INTEND – Children's Hospital Of Philadelphia Infant Test Of Neuromuscular Disorders; CNDR – Canadian Neuromuscular; HFMSE – Hammersmith Functional Motor Scale Extended; HINE - Hammersmith Infant Neurological Examination; NMSK – paediatric neuromuscular assessment; RULM – Revised Upper Limb Module; Disease Registry.

* If the child is developmentally capable of cooperating with this test.

Table A2.3 Surveillance recommendations for children with four SMN2 copies

	Months of age										
Assessment	0	3	6	9	12	18	24	36	48	60	72
NMSK	X	X	X	X	X	X	X	X	X	X	X
HINE	X	X	X	X	X	X	Stop when HFMSE initiated				
CHOP-INTEND	X	X	X	X	X	X	Continue if score < 50				
HFMSE							X	X	X	X	X
6MWT									X*	X*	X*
RULM									X*	X*	X*
CMAP	X	Repeat if clinically indicated									
EMG	X	Repeat if clinically indicated									
Treatment initiation	X Initiate treatment if clinical or neurophysiological signs of disease										

Key: 6MWT – 6 minute walk test; CHOP-INTEND – Children's Hospital Of Philadelphia Infant Test Of Neuromuscular Disorders; CMAP – compound muscle action potential; EMG – electromyography; CNDR – Canadian Neuromuscular; HFMSE – Hammersmith Functional Motor Scale Extended; HINE - Hammersmith Infant Neurological Examination; NMSK – paediatric neuromuscular assessment; RULM – Revised Upper Limb Module; Disease Registry.
* If the child is developmentally capable of cooperating with this test.

Appendix Chapter 4

Figure 4.1 PRISMA flow diagram

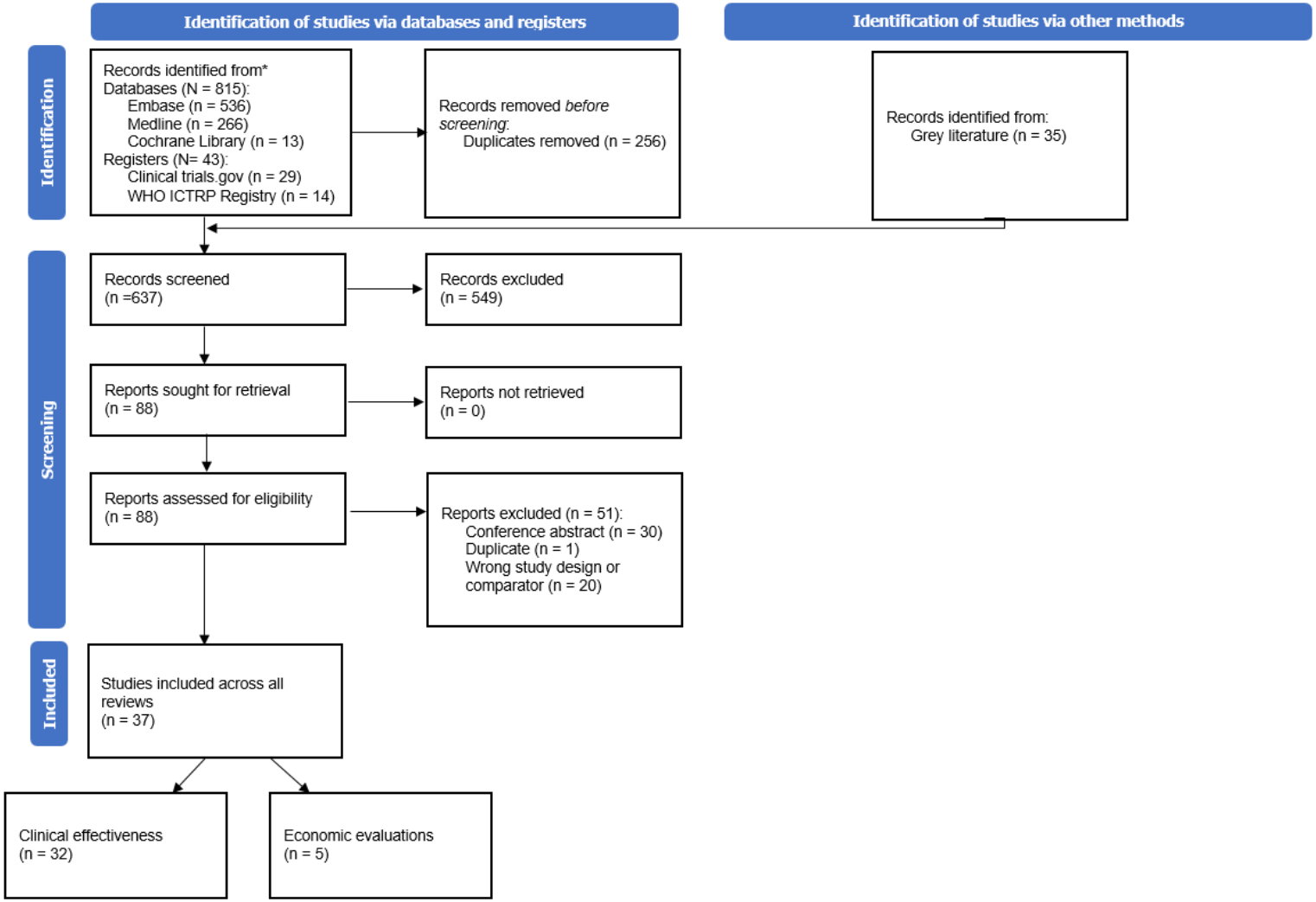


Table A4.1 Screening algorithms

Study	Target Cut-off	First tier	Second tier	Additional algorithm details	Confirmatory testing
Abiusi 2022	Homozygous deletions of *SMN1* Cut-off: Ct >=30	In-house developed assay with qPCR Control gene: NR	Not undertaken	NR	Neurological assessment of the child alongside confirmatory and prognostic molecular tests were performed on a fresh blood sample. Confirmation of homozygous *SMN1* deletion by RFLP-PCR *SMN2* copy number assessment by qPCR and identification of exon 7 splicing modifier variants.
Baker 2022	Homozygous *SMN1* exon 7 deletion Cut-off: NR	In-house assay with real-time PCR, multiplexed with SCID Control gene: RPP30	ddPCR assay (Bio-Rad) to assess *SMN2* copy numbers	Positive screens on first tier are further assessed for *SMN2* copy numbers by ddPCR with *SMN2* copy number included in screen-positive report.	Independent DBS collected for confirmation of homozygous *SMN1* exon 7 deletion and of *SMN2* copy number by ddPCR. SMA screen positive result are reported to the infants' primary care physician, and referred to a specialty centre where a paediatric neuromuscular specialist for the initial visit.
Boemer 2021 Additional reporting: Boemer 2019	Homozygous deletions of *SMN1* exon 7 Cut-off: NR	In house assay with qPCR Control gene: RPP30	Reanalysed twice with qPCR from the same DBS. Simultaneous MLPA undertaken using same DNA to confirm	NR	Referred to a neuro-paediatrician. Blood draw to confirm the positive screening result by MLPA. *SMN2* gene sequenced for the presence of intragenic

and Boemer 2019b			*SMN1* deletion and quantify *SMN2* copies		modifier variants (c.859G > C and c.835-44A > G).
D'Silva 2022 Additional reporting: Kariyawasam 2020	Homozygous deletion of exon 7 of *SMN1* and < 4 copies of *SMN2* on second tier testing	Perkin Elmer EONIS kit with real-time PCR. Multiplexed with TREC and KREC for immunodeficiencies(testing for SCID).	ddPCR on positive screens from first tier (quantified *SMN2* copy number)	Infants with *SMN1* deletion positivity and < 4 copies of *SMN2* on first DBS were considered screen-positive. >= 4 copies of *SMN2* not reported as screen positive as more likely to have a long latent phase, presenting with symptomatic SMA in late childhood or as adults.	All screen-positive newborns were invited to attend a centralized specialist neuromuscular service based. A second DBS to verify initial screen results and diagnostic blood tests on whole blood samples using MLPA were completed, alongside a neurological assessment.
Elkins 2022	Homozygous *SMN1* exon 7 deletion Cut-off: Ct >= 30	Assay with real-time PCR (cites CDC study) multiplexed with SCID. Initial positive Repeated in duplicate - if either duplicate elevated then considered positive screen Control gene: RPP30	Not undertaken	NR	Team contacts healthcare provider or child who assesses child and completes confirmatory testing which includes *SMN1* common deletion testing with reflex to *SMN2* copy number (method not reported)
Gailite 2022	Homozygous deletion *SMN1* exon 7 Cut-off: NR	CDC assay with qPCR. Retested in two independent runs. Control gene: RPP30	Non-applicable	NR	Referred and a blood sample taken at the first consultation with testing performed by qPCR and MLPA.

Hale 2021	Modifications of two independent CDC-developed qPCR-based assays, developed a multiplex, tiered testing algorithm Tier one: *SMN1* Exon 7 Tier two: *SMN1* Exon 7, *SMN1* Intron 7 Tier 2 provides explanation for failed amplification in Tier 1 (more sensitive) and prevents reporting of *SMN1* hybrids. Control gene: RNaseP Cut-off: NR	qPCR with assay A to detect absence of *SMN1* Exon 7	qPCR repeated with assay A and assay B targeting *SMN1* Exon 7, *SMN1* Intron 7	If all assay A replicates should absent Exon 7 but assay B showed present Exon 7 and absent Intron 7 then considered SMA hybrid and in normal range. If assay A and assay B show absent Exon 7 in all replicates then considered out of range and screen positive If all assay A replicates show absent Exon 7 and one or more assay B replicates show present Exon 7 then third tier of sequencing C nucleotide at position 840. If only T present then consider out range and screen positive. If C present then	Newborn bloodspot screening results provide initial *SMN2* copy analysis. Referred to primary care provider who contacts specialist and work together to obtain blood for diagnostic testing (type not reported).

				consider in normal range. Tier 3 sequencing also provides *SMN2* copy number for those referred to specialists.	
Kucera 2021	Homozygous deletion of *SMN1* at exon 7 Cut-offs: Ct >= 26 (initial), Ct >= 27 (retest)	Assay with qPCR (cites CDC study) Control gene:RPP30 Repeated in duplicate if above initial limits.	Not undertaken	If *SMN1* abnormal and RPP30 abnormal consider inclusive. If *SMN1* abnormal and RPP30 normal consider screen positive.	At initial clinical evaluation, whole blood specimen collected for *SMN1* and *SMN2* copy number testing with MLPA.
Kernohan 2021 Additional reporting: McMillan 2021 and supplementary data provided by authors	Bi-allelic disruption of *SMN1* (deletion or conversion) and four or fewer *SMN2* copies reported as positive.	In house MassARRAY test for presence of *SMN1* exon 7 SNV, and of exon 8 *SMN1* and *SMN2* SNVs. Involves initial PCR amplification of the relevant *SMN1* genomic region followed by annealing of primers overlapping or adjacent to sites of interest, with a single-base extension. Large multiplex MassARRAY panel including additional	MLPA on DBS for both *SMN1* and *SMN2* copy numbers	Children with more than four copies of *SMN2* are not reported	Referred to neurology specialist for evaluation and confirmatory molecular genetic testing (not specified) with fresh blood draw.

		genotyping for other conditions (early onset hearing loss and immunodeficiency)			
Kraszewski et al 2018	Carriers and homozygotes for the *SMN1* exon 7 deletion Cut-off: Ct >= 35	In-house assay with real-time PCR Control gene: RNaseP	Not undertaken	Specimens not meeting quality control criteria, or those with a homozygous/ heterozygous deletion, were rerun for confirmation using DNA extracted from a fresh dried bloodspot punch. To rule out allelic dropout due to the presence of interfering sequence variants in the *SMN1* primer or probe binding sites, all specimens with the *SMN1* deletion were sequenced. Amplification of RNAseP (Ct < 35) but not *SMN1* (Ct ≥ 35) was considered a homozygous	Referral and genetic testing (not specified)

				deletion; an average RQ = 0.300 - 0.599 was considered a heterozygous carrier; and an average RQ ≥ 0.800 was considered normal/no deletion	
Lee 2022 Additional reporting: Kay 2020	Homozygous deletion of *SMN1* at exon 7 Cut-off: Ct >= 30	Modified version of in-house qPCR assay described by Kraszewski et al. Modification of targets to exclude carriers.	*SMN2* copy number was determined in infants who screened positive using both the qPCR targeting *SMN2* exon 7 and a ddPCR kit. Results for *SMN2* were provided at the time of referral.	Samples with *SMN1* Ct ≥ 30 and RPPH1 Ct < 30 were considered screen positive.	Referred and confirmatory genetic testing completed (not specified)
Lin 2019	Homozygous *SMN1* deletion (c.840 and c.1155 nucleotides). Cut-off: NR	Agena iPLEX assay (MassARRAY genotyping platform based) Initial locus-specific PCR reaction, followed by single base extension using dideoxynucleotide terminators of a variant-specific oligonucleotide primer	Not undertaken	NR	MLPA
Matteson 2022	Homozygous deletion of	CDC assay with real time PCR	Positive screens also assessed with ddPCR to quantify *SMN1* and	RPP30 of Ct≤28 and *SMN1* Ct≥30 in the RT-PCR	SMA results usually post one business day after they are determined, at which point

	SMN1 at exon 7 Cut-off: Ct >= 30	Control gene: RPP30	*SMN2* copy numbers. Only *SMN1* results are reported to providers.	assay indicates a screen positive for SMA. A screen-negative is RPP30 of Ct ≤ 28 and *SMN1* of Ct < 30. A specimen with RPP30 of Ct ≥ 28 was considered incomplete. Both screen-positive and incomplete specimens are retested in triplicates on three fresh punches the next business day.	cases are assigned to area service centres who then notify primary care physicians and coordinate a referral to specialist for confirmatory testing through multiplex PCR/CE testing.
Noguchi 2022	Homozygous deletion exon 7 of *SMN1* Cut-off: NR	NeoSMAAT *SMN1* kit (Sekisui Medical Co) with qPCR	Not undertaken	NR	Referred to paediatricians, who examined the infant with confirmatory testing through MLPA and ddPCR on fresh blood draw
Sawada 2022	Homozygous deletion of exon 7 of *SMN1* Cut-off: NR	NeoSMAAT® *SMN1* kit (Sekisui medical Co) with real time PCR Control gene: RNaseP	Not undertaken	NR	Screen positives referred to paediatric department for evaluation and confirmatory testing through repeated assay and MLPA using whole blood draw.
Vill 2021 Additional reporting: Vill 2019, Czibere	Homozygous deletion of exon 7 of *SMN1*	Assay (not specified if laboratory developed) with qPCR (c.840C *SMN1*) Control gene: cystinosin	Not undertaken	An *SMN1* gene copy was considered present, if a product was	Positive screen referred to treatment centre where fresh whole blood sample collected for confirmation using MLPA (*SMN1* and *SMN2*).

2020, Muller-Felber 2020, Schwartz 2022, Kolbel 2022	Cut-off: Cq > 36			detected before Cq < 36, while the internal control was considered present if a Cq < 34 was detected. If no product was visible in any assay, the result was invalid. If only the control assay showed sufficient product, the result was considered positive. For invalid and initial positives, fresh DBS punches were retested.	Note: The methodology was changed to a different version of the original MLPA kit in February 2019. After misanalysis was uncovered in one patient, all samples were re-analysed with the newer kit in two independent laboratories
Weng 2021 Additional reporting: Chien 2017	Homozygous *SMN1* exon 7 deletion. Primers modified after pilot given first tier false positives detected. Cut-off: NR	Assay with real time PCR Control gene: RNaseP	ddPCR assay	Screen positive results from first tier assessed by ddPCR in second tier using same DBS	MLPA using fresh whole blood draw

Key: CDC – Centers for Disease Control and Prevention; DBS – dried bloodspot; ddPCR – digital droplet polymerase chain reaction; KREC – κ-deleting recombination excision circles; MLPA - multiplex ligation-dependent probe amplification; NA – non-applicable; NR – not reported; PPV – positive predictive

value; qPCR – quantitative polymerase chain reaction; SCID – severe combined immunodeficiency disease; SMA – spinal muscular atrophy; *SMN1* – survival motor neuron 1 gene*; SMN2* – survival motor neuron 2 gene; SNV – single nucleotide variant; TREC – T cell receptor excision circles.

Table A4.2 Treatment pathways described by included studies

Study	Decision-making criteria	Details of treatment pathway
Abiusi 2022	NR	On the same day as the 2nd tier test, the family was invited for a multidisciplinary counselling with medical geneticists and child neurologists to provide information regarding SMA and therapeutic options and to perform the first neurological assessment of the child alongside confirmatory and prognostic testing. Within a few days, the family was provided with the official report of the genetic tests, in the context of a second multidisciplinary counselling aimed at providing information regarding prognostic elements, therapeutic options and reproductive risk for the couple and their families. ▪ Patients with two or three copies of *SMN2* were treated immediately ▪ Patients with > 4 copies of *SMN2* were included in a strict clinical follow-up to detect and treat at the first signs of the disease.
Baker 2022	NR	During initial visit, family was counselled about SMA, confirmatory testing, and treatments. Families are informed about three FDA approved disease-modifying treatments, with two approved for infants under two months of age, OA and nusinersen. Additionally, at the second clinic visit, there were discussions about future pregnancies and extended-family risk of having children with SMA.
Boemer 2021 Additional reporting: Boemer 2019 and Boemer 2019b	Cites Glascock et al 2018: 2/3 *SMN2* copies provide immediate treatment 4 or more copies of *SMN2* monitor and treat at onset of symptoms	At the time of the study, in Belgium: ▪ nusinersen was reimbursed for patients with two or three copies of *SMN2*. ▪ Patients could also be included in the SPR1NT gene therapy trial for presymptomatic cases. ▪ Patients with four copies could either opt for clinical surveillance or inclusion in risdiplam presymptomatic trial.
D'Silva 2022 Additional reporting: Kariyawasam 2020	Cites that the newborn bloodspot screening programme for SMA involved collaboration among multiple stakeholders across policy, diagnostic, and health-care systems.	Australian health regulations at time of study allowed licensed and reimbursed nusinersen therapy for symptomatic individuals (< 18 years of age and with symptom onset < 3 years) only. Individuals with *SMN1* deletion and ≥ 4 copies of *SMN2* are more likely to have a long latent phase, presenting with symptomatic SMA in late childhood or as adults. Thus, these individuals were not reported by research pilot screening program to avoid possible psychological harm caused by providing an early diagnosis, with no immediate option for therapeutic intervention in Australia. The paediatrician named on the DBS card and an assigned neuromuscular

	Incorporates Calucho 2018 prognostic *SMN2* copy numbers	specialist were contacted by the newborn bloodspot screening laboratory to flag the screen-positive result. After communication and delegation of roles between the paediatrician and specialist, the family was contacted by the assigned clinician and advised (over the telephone) of a screen-positive result for a neuromuscular disorder. All screen-positive newborns were invited to attend a centralised specialist neuromuscular service based. A second DBS to verify initial screen results and diagnostic blood tests were completed, alongside a neurological assessment. The family was supported by the neuromuscular specialist, a genetic counsellor, and a social worker. Once diagnostic results were available the family was invited back to clinic to discuss the implication of diagnostic results and next steps for management. Multidisciplinary review and clinical follow-up were facilitated from this point. Due to the high probability of early disease onset, (as predicted by *SMN2* copy number) and to support decision making, repeated clinical assessment and electrophysiological measures (CMAP and electromyography) were conducted by a paediatric neuromuscular specialist to detect early features of disease onset while treatment was being planned in presymptomatic neonates. Parents were counselled on genotype–phenotype correlation in SMA, allowing them to make informed decisions on management strategies for their newborn. Using data from previously published studies on *SMN2* copy number, they were counselled that: ▪ untreated presymptomatic newborns with two *SMN2* copies would have type 1 (would never sit) or 2 (would never walk) phenotype in approximately 82% and 17.2% of cases respectively. ▪ untreated presymptomatic newborns with three *SMN2* copies would have severe phenotypes (SMA type 1 and 2) in 17% and 70% of cases respectively. This guidance allowed families to consider proactive intervention by being enrolled into a presymptomatic clinical trial (risdiplam or OA) or starting approved therapy on an individual compassionate basis. Alternatively, families were given the option of choosing a supportive model of care alone and/or starting disease-modifying treatments in response to symptom onset. Cascade testing for older siblings and carrier testing for parents offered.
Elkins 2022	NR	Referred to Neurology specialists. Therapeutic intervention options which were available at the time

		(nusinersen, risdiplam, and OA) were reviewed with families. Treatment was performed based on family decision in consultation with the treatment team. Families were offered genetic counselling and evaluated by a medical geneticist.
Gailite 2022	NR	Reports general protocols in Latvia in that treatment can be initiated with nusinersen and risdiplam in the following patient groups: ▪ patients with molecularly confirmed pre-symptomatic SMA with two or three *SMN2* copies ▪ SMA type I patients with two *SMN2* copies under six months of age ▪ SMA type I patients with three *SMN2* copies under eight months of age ▪ SMA type II and III patients with two and more *SMN2* copies under 18 years of age.
Hale 2021	Cites Glascock et al 2018 and 2020 recommendations	Specialist reports diagnostic test results to newborn bloodspot screening programme and family, and treatment was initiated. Original treatment guidelines required that *SMN2* copy number be no greater than 3. More recent treatment guidelines do not require limits to the copy number of *SMN2* for treatment.
Kernohan 2021 Additional reporting: McMillan 2021 and supplementary data provided by authors	Series of teleconferences culminating in a 1-day face-to-face meeting, Ontario-based Paediatric Neuromuscular disease experts reviewed and discussed the evidence, expert consensus statements, provincial and national treatment reimbursement guidelines, and clinical practice regarding diagnosis and treatment of children with SMA as it pertained to newborn bloodspot screening	*SMN1*-null infants with four or fewer copies of *SMN2* would be classified "screen positive". The group agreed that while the natural history of infants with five *SMN2* copies or more was not wholly predictable, adult-onset disease or potentially remaining completely asymptomatic throughout his or her life was the most likely outcomes. As such, reporting this condition when there is a chance that disease manifestation may not occur was deemed to be unethical and not in patients' best interest given the potential psychosocial impact, exclusion from insurability, and other potential ramifications associated with this disclosure. Infants with *SMN1* with bi-allelic disruption and four *SMN2* copies or less would be referred to a regional treatment centre. A trained genetic counsellor or nurse would contact the infant's family by telephone and they would either be directed to the closest paediatric hospital or have blood sent for confirmatory SMA genetic testing to be performed and to meet with a paediatric neuromuscular specialist to discuss the potential implications of the NSO test result. Following diagnostic confirmation, and determination of *SMN2* copy number, infants, and their families are assessed by a paediatric neuromuscular specialist at which time the family would have an opportunity to discuss treatment options and standard of care guidelines that are followed at all Ontario Pediatric Neuromuscular

		clinics. Baseline functional assessments (CHOP-INTEND, HINE-II) would be performed by a trained physiotherapist or clinical evaluator at or around that time. ▪ **1 *SMN2* copy:** predictive of SMA type 0 would be evaluated immediately. Given the potential severity of this congenital-onset form of SMA which could include the need for mechanical ventilation, the pediatric neuromuscular physician and family would discuss potential treatment options. ▪ **2 or 3 *SMN2* copies:** All infants with two or three *SMN2* copies, given the evidence for rapid and irreversible loss of motor neurons, were recommended for immediate initiation of disease-modifying treatments prior to any clinical symptom onset (recommendation is concordant with Ontario's Exceptional Access Program reimbursement criteria for nusinersen). Ongoing surveillance through structured measures dependent on age. ▪ **4 *SMN2* copies:** Neuromuscular assessment as cannot rule out type I or II, motor nerve studies also recommended. Any clinical sign of SMA on neuromuscular examination (i.e. weakness, hypotonia, hyporeflexia, etc.) or neurophysiological evidence through nerve studies would prompt initiation of disease-modifying treatment. If no SMA signs then treatment not be initiated and the child be seen every 3 months until 12 months of age with structured outcome measures dependent on age. Intervals then extend and outcome measures change with child seen at 18 months, 24 months, and annually from there on.
Kucera 2021	NR	Screen-positive results were reported by the laboratory staff to the clinical genetics follow-up team. Genetic counsellor contacts family and then arranges specialist follow up. Specialist completes clinical exam and sends sample for confirmatory testing. Parent's mental health and family well-being assessed. Parents provided counselling about treatment options.
Kraszewski et al 2018	NR	Parents of one infant homozygous for the *SMN1* deletion were notified by the study principal investigator, a medical geneticist, and asked to immediately come to the Columbia University Spinal Muscular Atrophy Clinical Research Center for evaluation and education about treatment options. A genetic counsellor called all parents of heterozygous carriers of the *SMN1* exon 7 deletion, and a letter

		documenting the results was mailed to families. Parents had the option of meeting with the genetic counsellor and having genetic testing to determine if both parents were carriers for future family planning.
Lee 2022 Additional reporting: Kay 2020	NR	Infants were referred to NYS Neuromuscular SCCs for facilitation of diagnostic confirmation, clinical evaluation, and treatment.
Lin 2019	NR	NR
Matteson 2022	NR	Referral to specialist neuromuscular care who provide genetic counselling, order confirmatory testing, determine a case resolution, and coordinate treatment, if necessary.
Noguchi 2022	NR	NR
Sawada 2022	NR	NR
Vill 2021 Additional reporting: Vill 2019, Czibere 2020, Muller-Felber 2020, Schwartz 2022, Kolbel 2022	Cites Glascock et al 2018: protocol provided for a treatment decision in accordance with the recommendations of the "American SMA NBS Multidisciplinary Working Group," published in 2018	In case of a positive screening result, the respective treatment centre for SMA (Munich, Essen or Münster) was informed by the screening laboratory. Parents were contacted by the treatment centre and an immediate appointment, usually on the following day, was offered for information and confirmation of diagnosis and *SMN2* copy number determination. ▪ Immediate treatment with nusinersen was recommended to children with 2 and 3 *SMN2* copies. OA not licensed in Europe at the time of study. ▪ A "watchful waiting" strategy was used with children with ≥4 copies of *SMN2*. Every 2 to 4 months, patients underwent regular standardised neuropediatric examination, comprising electrophysiological exams, CHOP-INTEND and the HINE-2. Children with normal muscle tone, a CHOP-INTEND score of > 35 points, an ulnar CMAP amplitude > 1 mV and no deterioration in their first 4 weeks of life were considered pre-symptomatic.
Weng 2021 Additional reporting: Chien 2017	NR	▪ Two copies of *SMN2* were treated immediately after the diagnosis (clinical trials and expanded use) ▪ Three copies of *SMN2* were followed monthly for symptom onset before starting treatment, ▪ Four copies of *SMN2* were evaluated in outpatient clinics or followed by phone every 4 to 6 months. The evaluations included neurological examinations, developmental milestones, and CMAP, of which the maximal CMAP amplitude of the ulnar nerve was recorded by experienced paediatric neurologists.

Key: CHOP-INTEND - Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; CMAP - compound motor action potential; IQR – interquartile range; DBS – dried bloodspot; HINE -

Hammersmith Infant Neurological Examination; NBS – newborn bloodspot screening; NR – not reported; OA – onasemnogene abeparvovec; SMA – spinal muscular atrophy; *SMN2* – survival motor neuron 2 gene.

Table A4.3 Treatment status of reported SMA cases

Study	Number of cases	Number receiving treatment by type
Non-comparative studies		
Boemer 2021	9	▪ OA: n = 2 ▪ Nusinersen: n = 6 ▪ Risdiplam: n = 1
Abiusi 2022	15	▪ Disease modifying treatments (not specified): n = 13 (one, two, three copies of *SMN2*) ▪ Not treated (monitoring): n = 2 (four and six copies of *SMN2*)
Baker 2022	6	▪ OA: n = 5 ▪ Nusinersen: n = 1 (due to AAV9 titres)
Elkins 2022	15	▪ OA: n = 9 ▪ Nusinersen: n = 1 (delayed as missed case) ▪ Not treated (monitoring): n = 2 (>= 4 copies of *SMN2*) ▪ Deceased prior to treatment: n = 4 (two with one *SMN2* copy, two with two copies of *SMN2*)
Gailite 2022	2	▪ One case received treatment (unspecified) ▪ One type 0 case for whom no treatment was initiated subsequently died
Hale 2021	9	▪ OA: n = 5 ▪ Nusinersen: n = 2 ▪ OA/nusinersen/risdiplam: n = 1 ▪ OA/nusinersen: n = 1
Kucera 2021	1	▪ Nusinersen: n = 1 (AAV9 titres precluded OA)
Matteson 2022	34	▪ OA: n= 29 ▪ Nusinersen: n = 3 ▪ OA and Nusinersen: n = 1 ▪ Deceased prior to treatment: n = 1 (2 copies of *SMN2*)
Lin 2019	3	▪ Not treated as no treatments were available in China at the time
Weng 2021 Additional reporting: Chien 2017	20	**Two copies of *SMN2* eligible for immediate treatment (n = 9):** ▪ Nusinersen: n = 4 ▪ OA: n = 2 ▪ Deceased: n = 3 **Three copies of *SMN2* treated at onset (n = 5):** ▪ Nusinersen: n = 4 ▪ Untreated: n = 1 **Four copies of *SMN2* (n = 6):** ▪ Untreated at time of write up (n = 6)

Study	Number of cases	Number receiving treatment by type
Kernohan 2021 Additional reporting: McMillan 2021	5	▪ Nusinersen: n = 3 (all 2 *SMN2* copies) ▪ Parents declined treatment: n = 1 (3 *SMN2* copies) ▪ Ongoing surveillance: n = 1 (4 *SMN2* copies, asymptomatic at time of writing)
Kraszewski et al 2018	1	Single patient received nusinersen
Lee 2022 Additional reporting: Kay 2020	34	**One *SMN2* copy (n = 1)** ▪ Risdiplam: n = 1 **Two *SMN2* copies (n = 18)** ▪ OA: n = 11 ▪ Nusinersen/OA: n = 4 ▪ Nusinersen: n = 1 ▪ OA/Risdiplam: n = 2 **Three *SMN2* copies (n = 11)** ▪ OA: n = 10 ▪ Nusinersen/OA: n = 1 **Four *SMN2* copies (n = 2)** ▪ OA: n = 1 ▪ Surveillance: n = 1 **Five *SMN2* copies (n = 2)** ▪ OA: n = 1 ▪ Surveillance: n = 1
Sawada 2022	1	Single patient received OA
Noguchi 2022	2	▪ Nusinersen: n = 1 ▪ Nusinersen/OA: n = 1
Vill 2021 Additional reporting: Vill 2019, Czibere 2020, Muller-Felber 2020, Schwartz 2022, Kolbel 2022	43	**Two *SMN2* copies (n = 17)** ▪ Nusinersen: n = 15 ▪ Parental refusal: n = 1 ▪ Treatment not reimbursed: n = 1 **Three *SMN2* copies (n = 10)** ▪ Nusinersen: n = 7* ▪ Parental refusal: n = 3 **Four *SMN2* copies (n = 14)** ▪ Nusinersen: n = 2** ▪ Not treated: n = 12 **Five *SMN2* copies (n = 2)** ▪ Not treated: n = 2 *one patient initially misquantified as 4 copies **one patient developed symptoms within 8 months, second patient had family history and patient's elected to treat
D'Silva 2022 Additional reporting:	21	Only reported for nine cases up to July 2019: ▪ Presymptomatic treatment trial (OA or Risdiplam): n = 5 ▪ Nusinersen: n = 3 ▪ Supportive care: n = 1

Study	Number of cases	Number receiving treatment by type
Kariyawasam 2020		
Comparative studies		
Kariyawasam 2023[153]	Screening: n = 15 Comparator: n = 18	Screening: ▪ Nusinersen: n = 8 (53%) ▪ OA: n = 5 (33%) ▪ Palliative care pathway: n = 1 (7%) ▪ Active surveillance: n = 1 (7%) Comparator: ▪ Nusinersen: n = 16 (89%) ▪ Palliative care pathway: n = 2 (11%)
Dangoulouff 2022[154]	Not identified by symptoms: n = 14 Treated symptomatic patients: n = 42	Not identified by symptoms: ▪ Nusinersen: n = 7 (50%) ▪ OA: n = 4 (29%) ▪ Risdiplam: n = 3 (21%) Treated symptomatic patients: ▪ Nusinersen: n = 31 (74%) ▪ OA: n = 6 (14%) ▪ Risdiplam: n = 5 (12%)
Chan 2021[130]	40	Nusinersen: n = 40 (100%)

Key: AAV9 - adeno-associated virus 9; OA – onasemnogene abeparvovec; *SMN2* – survival motor neuron 2 gene.

Table A4.4 Laboratory turnaround times

Study	Laboratory turnaround times
Boemer 2021 Additional reporting: Boemer 2019 and Boemer 2019b	▪ 2018 one lab: Median 7.2 days (IQR: 6.0 to 9.0 days) ▪ 2019 new equipment: Median 4.0 days (IQR: 2.5 to 5.9 days) ▪ 2020: Median 2.7 days (IQR: 2.0 to 4.7 days)
Abiusi 2022	NR
Baker 2022	Median age newborn bloodspot screening reporting: 3 days (range 3 to 6)
Elkins 2022	▪ Median age newborn bloodspot screening reporting: 5 days (range 1 to 6) ▪ Median time from NBS result to confirmatory result: 3 days (range 0 to 19)
Gailite 2022	▪ Median time to report NBS results: 4 +/- 2.3 days ▪ Median age newborn bloodspot screening result: 11 +/- 4.5 days
Hale 2021	▪ Median time to report NBS results: 1 day (range 0 to 3) ▪ Median age newborn bloodspot screening result: 4 days (range 3 to 6)
Kucera 2021	▪ Median return of NBS results: 13 days after birth (prenatally enrolled) and 21 days after birth (postnatally enrolled) ▪ Mean time from NBS results to reporting to parents: 5.47 +/- 2.32 days (prenatally enrolled) and 4.68 days +/- 2.64 days (postnatally enrolled)
Matteson 2022	Median time to newborn bloodspot screening results reported: median 7 days (range 4 to 14)
Lin 2019	NR
Weng 2021 Additional reporting: Chien 2017	NR
Kernohan 2021 Additional reporting: McMillan 2021	Median age when referred to treatment centre: 9 days (range 6 to 15 days)
Kernohan 2023 Unpublished data provided by authors	Median age when referred to treatment centre: 9.5 days (range 6 to 15)
Kraszewski et al 2018	NR

Study	Laboratory turnaround times
Lee 2022 Additional reporting: Kay 2020	Median age when newborn bloodspot screening reported: 7 days (range 4-12)
Sawada 2022	Single patient initial visit 14 days
Noguchi 2022	Patient 1: 21 days Patient 2: 17 days
Vill 2021 Additional reporting: Vill 2019, Czibere 2020, Muller-Felber 2020, Schwartz 2022, Kolbel 2022	Median age positive results reported: 6 days (range 3 to 9 days)
D'Silva 2022 Additional reporting: Kariyawasam 2020	Median age: 3 days (range 2 to 15)

Key: IQR – interquartile range; NBS – newborn bloodspot screening; NR – not reported.

Appendix Chapter 5

Table A5.1 Registered trials for the EMA-authorised, SMN-dependent treatments

Trial name NCT	Trial design	Completion date
Nusinersen		
NURTURE NCT02386553	Phase II, open-label, single group assignment, no control arm	January 27, 2025 (estimated)
CS3A NCT01839656	Phase II, dose-escalating, open label	August 21, 2017
ENDEAR NCT02193074	Phase III, quadruple-blind, sham-control	November 21, 2016
CS1 NCT01494701	Phase I, open-label, no control arm	January 31, 2013
CS10 NCT01780246	Phase I, open-label, no control arm	February 28, 2014
CS2 NCT01703988	Phase I and II, open-label, no control arm	January 31, 2015
CS12 NCT02052791	Phase I, open-label, no control arm	January 31, 2017
CHERISH NCT02292537	Phase III, quadruple blind, sham-control	February 20, 2017
DEVOTE NCT04089566	Phase II and III, double blind, escalating dose nusinersen	July 28, 2023 (estimated)
SHINE NCT02594124	Phase III, triple blind (during loading phase), no control arm	August 29, 2023 (estimated)
ASCEND NCT05067790	Phase III, open-label, no control arm	June 14, 2027 (estimated)
RESPOND NCT04488133	Phase IV, open-label, no control arm	September 4, 2024 (estimated)
Onasemnogene Abeparvovec		
SPR1NT NCT03505099	Phase III, open-label, single group assignment, no control arm	June 15, 2021
STR1VE-US NCT03306277	Phase III, open-label, single group assignment, no control arm	November 12, 2019
START NCT02122952	Phase I, open-label, no control arm	December 15, 2017
NCT03421977	Long term follow up study	December 2033 (estimated)
STR1VE-EU NCT03461289	Phase III, open-label, no control arm	September 11, 2020
NCT04042025	Long term follow up study	December 29, 2035 (estimated)
SMART NCT04851873	Phase III, open-label, no control arm	November 2, 2023 (estimated)

Trial name NCT	Trial design	Completion date
STRONG NCT03381729	Phase I, open-label, no control arm	November 18, 2021
STEER NCT05089656	Phase III, crossover, quadruple blind, sham-control	October 21, 2024 (estimated)
Risdiplam		
RAINBOWFISH NCT03779334	Phase II, open-label, single group assignment, no control arm	January 21, 2029 (estimated)
FIREFISH NCT02913482	Phase II/III, open-label, sequential assignment, no control arm	November 17, 2023 (estimated)
SUNFISH NCT02908685	Phase II/III, double blind, sequential assignment, sham controlled	September 2, 2023 (estimated)
JEWELFISH NCT03032172	Phase II, open-label, no control arm	December 27, 2024 (estimated)

Table A5.2 Quality appraisal of systematic review by Erdos et al. 2022 using AMSTAR 2 critical appraisal tool

Domain	Rating
1. Did the research questions and inclusion criteria for the review include the components of PICO?	Yes
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	Partial Yes
3. Did the review authors explain their selection of the study designs for inclusion in the review?	No
4. Did the review authors use a comprehensive literature search strategy?	Partial Yes
5. Did the review authors perform study selection in duplicate?	Yes
6. Did the review authors perform data extraction in duplicate?	No
7. Did the review authors provide a list of excluded studies and justify the exclusions?	No
8. Did the review authors describe the included studies in adequate detail?	Partial Yes
9. Did the review authors use a satisfactory technique for assessing the risk of bias in individual studies that were included in the review?	Yes
10. Did the review authors report on the sources of funding for the studies included in the review?	Yes
11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	No meta-analysis conducted
12. If meta-analysis was performed, did the review authors assess the potential impact of risk of bias in individual studies on the results of the meta-analysis or other evidence synthesis?	No meta-analysis conducted
13. Did the review authors account for risk of bias in individual studies when interpreting/ discussing the results of the review?	Yes
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	No
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	No meta-analysis conducted
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes

A5.1 Detailed results of trials of presymptomatic initiation of treatment

1. Nusinersen

NURTURE[187]

Trial description

NURTURE is an ongoing international, open-label, single arm, Phase II trial that aims to evaluate the safety and efficacy of intrathecal nusinersen in infants who initiate treatment prior to the onset of symptoms of SMA. Eligible infants must have been less than or equal to six weeks of age at first dose, have genetically confirmed SMA (with either homozygous deletion or a compound heterozygous variant, that is, a deletion on one chromosome and a pathogenic variant on the other), two or three copies of *SMN2*, and baseline compound muscle action potential (CMAP) amplitude ≥1 mV. When possible, comparisons were made between trial participants and siblings with SMA who were not treated with nusinersen. Additional details of characteristics and results are summarised in Tables A5.1 and A5.2.

Results

Results are reported below for a published interim analysis with a data-cut off of 29 March 2019 representing a median follow-up of 2.9 years.

Baseline characteristics

A total of 25 participants were included in the trial, 15 of whom had two copies of *SMN2*, and 10 who had three copies of *SMN2*. Overall, the median age at treatment initiation was 22 days (range 3 to 42) and 48% were male. When possible, comparisons were made between trial participants and siblings with SMA who were not treated with nusinersen. Nineteen participants had one or more siblings with SMA who were not treated with nusinersen. This included 24 siblings, eight of whom had two *SMN2* copies, eight had three *SMN2* copies, and eight had an undocumented number of *SMN2* copies.

Efficacy endpoints

Primary endpoint: The primary endpoint was defined as time to death or respiratory intervention. At the time of the interim analysis, all participants were alive without the requirement for permanent ventilation. The median time to death or respiratory intervention could not be estimated as there were too few events. A total of 16% (n=4) of participants, all with two copies of *SMN2,* required respiratory intervention with this treatment initiated during an acute reversible illness. At the last study visit prior to the data cut-off for the interim analysis, two of the participants no longer used respiratory intervention.

Secondary endpoints: For the WHO motor milestones "sitting without support", "walking with assistance", and "walking alone", 25 (100%), 23 (92%), and 22 (88%) participants, respectively, obtained the milestone. The participants who did not obtain the milestones had two copies of *SMN2.* HINE-2 motor milestone total scores increased over time for all participants, approaching the scale maximum of 26 points, with participants with three copies of *SMN2* approaching the maximum earlier than those with two copies. In terms of motor function endpoints as assessed by CHOP-INTEND, total scores rose steadily from baseline until approximately day 183 and then remained stable over time. Beyond this point, the scores appeared to plateau.

By the 13-month time point, ten of the participants with two copies of *SMN2* and two of the participants with three copies of *SMN2* had protocol-defined symptoms of SMA, which decreased to seven and no participants, respectively, by the 24-month time point (meaning that these participants no longer met the protocol-defined criteria for clinically manifested SMA). The seven infants who developed symptoms of SMA by 24 months (all of whom had two copies of *SMN2*) were all continuing to grow and achieve WHO motor milestones. This differs from typical milestones observed in infants with type I SMA, and also contrasted with the milestone attainment of their siblings with SMA. All seven were sitting without support, five were walking with or without assistance, and four were walking alone. Six of these seven participants had siblings with SMA; none of the siblings achieved the milestone of sitting independently and five required tracheostomy and/or died by 16 months of age.

Safety endpoints

All (100%) of participants experienced an adverse event, 12 (48%) experienced a serious adverse event, and five (20%) experienced a severe adverse event (both as defined by the study authors). A total of eight (32%) participants experienced an adverse event possibly related to the study drug. No serious adverse event was considered as related to treatment with nusinersen.

Table A5.3 Summary of NURTURE (nusinersen - presymptomatic initiation) trial baseline characteristics

Characteristic		2 *SMN2* copies (n = 15)	3 *SMN2* copies (n = 10)	Total (n = 25)
Age at first dose, days	≤ 14 days	n = 6 (40%)	n = 3 (30%)	n = 9 (36%)
	> 14 days and ≤ 28 days	n = 7 (47%)	n = 5 (50%)	n = 12 (48%)
	> 28 days	n = 2 (13%)	n = 2 (20%)	n = 4 (16%)
	Median (range)	19.0 (range 8 to 41)	23.0 (range 3 to 42)	22.0 (range 3 to 42)
	Mean (SD)	19.5 (SD 9.29)	22.3 (SD 12.45)	20.6 (SD 10.51)
Sex	Male	n = 8 (53%)	n = 4 (40%)	n = 12 (48%)
	Female	n = 7 (47%)	n = 6 (60%)	n = 13 (52%)
CHOP-INTEND total score	Number of scores obtained	15	10	25
	Median	45.0 (range 25.0 to 60.0)	53.5 (range 40.0 to 60.0)	50.0 (range 25.0 to 60.0)
	Mean	47.0 (SD 10.04)	51.9 (SD 6.10)	49.0 (SD 8.87)
HINE total motor milestones	Number of scores obtained	15	10	25
	Median	3.0 (range 0 to 5)	3.0 (range 0 to 7)	3.0 (range 0 to 7)
	Mean	2.7 (SD 1.59)	3.2 (SD 1.87)	2.9 (SD 1.69)
Ulnar CMAP amplitude, mV	Number of scores obtained	14	10	24
	Median	2.30 (range 1.0 to 6.7)	2.90 (range 1.8 to 4.9)	2.65 (range 1.0 to 6.7)
	Mean	2.69 (SD 1.516)	3.11 (SD 1.119)	2.87 (SD 1.354)

Characteristic		2 *SMN2* copies (n = 15)	3 *SMN2* copies (n = 10)	Total (n = 25)
Peroneal CMAP amplitude	Number of scores obtained	12	10	22
	Median	3.20 (range 1.1 to 9.7)	4.00 (range 0.2 to 7.0)	3.30 (range 0.2 to 9.7)
	Mean	3.52 (SD 2.159)	3.75 (SD 2.188)	3.62 (SD 2.123)
Plasma pNF-H, pg/mL	Number of measurements obtained	13	9	22
	Geometric mean	20880.9 (95% CI 9639.4 to 45231.9)	1870.7 (95% CI 1152.9 to 3035.5)	7782.7 (95% CI 3828.6 to 15820.3)
	Range	845 to 52,900	959 to 7950	845 to 52,900
CSF pNF-H, pg/mL	Number of measurements obtained	14	9	23
	Geometric mean	20139.2 (95% CI 10075.0 to 40256.7)	951.5 (95% CI 366.5 to 2470.2)	6099.8 (95% CI 2646.0 to 14062.0)
	Range	342 to 37200	261 to 9140	261 to 37200

Key: CHOP-INTEND - Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; CMAP - compound muscle action potential; CSF – cerebrospinal fluid; HINE - Hammersmith Infant Neurological Examination; pNF-H - phosphorylated neurofilament heavy chain; SD - standard deviation; *SMN2* – survival motor neuron 2 gene.
Sources: De Vivo et al.[187]

Table A5.4 Summary of NURTURE (nusinersen – presymptomatic initiation) trial efficacy endpoint results

Endpoint		2 *SMN2* copies (n = 15)	3 *SMN2* copies (n = 10)	Total (n = 25)
Primary endpoint				
Death or respiratory intervention*	Number	n = 4 (27%)	n = 0 (0%)	n = 4 (16%)
Secondary endpoints				
Alive	Number	n = 15 (100%)	n = 10 (100%)	n = 25 (100%)
WHO motor milestone "sitting without support"	Number achieved	n = 15 (100%)	10 (100%)	n = 25 (100%)
	Median age for first achievement, months	7.9 (95% CI 5.9 to 9.2)	6.4 (95% CI 5.1 to 7.9)	NR
	Number achieving within WHO window for healthy children†	n = 11 (73%)	n = 10 (100%)	n = 21 (84%)
WHO motor milestone "walking with assistance"	Number achieved	n = 13 (87%)	n = 10 (100%)	n = 23 (92%)
	Median age for first achievement, months	16.1 (95% CI 11.8 to 18.8)	9.6 (95% CI 8.0 to 11.8)	NR
	Number achieving within WHO window for healthy children†	n = 5 (33%)	n = 10 (100%)	n = 15 (60%)
WHO motor milestone "walking alone"	Number achieved	n = 12 (80%)	10 (100%)	22 (88%)
	Median age for first achievement, months	20.4 (95% CI 15.5 to 29.7)	12.3 (95% CI 11.2 to 14.9)	NR

Endpoint		2 *SMN2* copies (n = 15)	3 *SMN2* copies (n = 10)	Total (n = 25)
	Number achieving within WHO window for healthy children†	n = 6 (40%)	n = 10 (100%)	n = 16 (64%)
HINE-2 motor milestone total scores at last observed visit	Mean	23.9 (range 16 to 26)	26.0 (range 26 to 26)	NR
CHOP-INTEND total score	Mean	62.1 (range 48 to 64)	63.4 (range 58 to 64)	NR
	Number achieving maximum score	n = 10 (67%)	n = 10 (100%)	NR
HINE-1 assessment of ability to suck and swallow	Number achieving ability to suck and swallow	n = 15 (100%)	n = 10 (100%)	n = 25 (100%)
	Number achieving maximum score	n = 12 (80%)	n = 10 (100%)	n = 22 (88%)
Development of clinically manifested SMA	Number at 13-month time point	n = 10	n = 2	NR
	Proportion at 13-month time point	0.67 (95% CI 0.39 to 0.87)	0.20 (95% CI 0.04 to 0.56)	NR
	Number at 24-month time point	n = 7	n = 0	NR
	Proportion at 24-month time point	0.47 (95% CI 0.22 to 0.73)	0.00 (95% CI 0.00 to 0.24)	NR

Key: CHOP-INTEND – Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; CI – confidence interval; HINE – Hammersmith Infant Neurological Examination; SD – standard deviation; SMA – spinal muscular atrophy; *SMN2* – survival motor neuron 2 gene; WHO - World Health Organization.

* Median time to death or respiratory intervention could not be estimated due to the limited number of events.
† Achievement within the WHO 99th percentile for healthy children.
Sources: De Vivo et al.(187)

2. Onasemnogene abeparvovec

SPR1NT[188, 189]

SPR1NT was an international, open-label, single arm, Phase III trial that aimed to evaluate the safety and efficacy of OA in infants with genetically confirmed SMA initiated prior to clinical disease onset.[188, 189] Eligible infants must have been less than or equal to six weeks of age at first dose and have CMAP ≥2mV at baseline. Two cohorts were enrolled;

- Cohort one had two copies of *SMN2*: In the absence of treatment almost all participants were likely to develop SMA type I with very small numbers expected to develop SMA type II or type III.
- Cohort two had three copies of *SMN2*: In the absence of treatment, around half of these participants were likely to develop, SMA type II with the remainder developing type I or type III.

Additional details of characteristics and results are summarised in Tables A5.5 and A5.6.

Results[188, 189]

Baseline characteristics

A total of 14 and 15 participants were included in cohort one and cohort two respectively. The median ages at dosing of OA in cohort one and cohort two were 21 days and 32 days, respectively. Follow-up was up to 18 months in cohort one and 24 months in cohort two.

Efficacy outcomes: Cohort one (two copies of *SMN2*)[188]

Primary endpoint: The primary endpoint of independent sitting for at least 30 seconds at any visit up to 18 months of age was attained by all participants (n = 14, 100%). The median age of attainment was 265 days (range 172 to 354), with 11 (78%) participants attaining the milestone within the WHO normal development range. Additionally, by 18 months, 11 (79%) participants were able to stand alone and nine (64%) participants were able to walk independently, with seven (50%) and five (36%) of these, respectively, achieving the milestone within the normal development window.

Secondary endpoints: All participants (n = 14, 100%) were event-free (meaning, no death or requirement for permanent ventilation in the absence of acute illness or peri-operatively) at 14 months of age. None of the participants required any kind of mechanical respiratory support throughout the trial.

Additionally, 13 (93%) participants were able to maintain weight at or above the third percentile without the need for non-oral/mechanical feeding support up to age of 18 months. All 14 (100%) participants remained free of non-oral or mechanical feeding support throughout the trial. A total of 12 (86%) children were considered as thriving at the 18-month study visit.

Efficacy outcomes: Cohort 2 (three copies of *SMN2*)[189]

Primary endpoint: The primary endpoint of independent standing for at least three seconds at any visit up to 24 months of age was attained by all participants (n = 15, 100%). The median age of attainment was 12.6 months (range 9.5 to 18.3), with 14 (93%) participants attaining the milestone within the WHO normal development range. All participants maintained this milestone past the 24-month study visit.

Secondary endpoints: A total of 14 (93%) participants walked independently for at least five steps at any visit up to 24 months of age, with 11 (73%) achieving the milestone within the normal development window.

Safety outcomes

In cohort one, a total of 159 treatment-emergent adverse events were reported, with all participants experiencing at least one event, five (36%) participants experiencing an event reported as serious. While ten (71%) experienced an event that was considered to be related to the study treatment none of the events were reported as serious.[188]

In cohort two, a total of 166 treatment-emergent adverse events were reported, with all participants experiencing at least one event, three (20%) participants experiencing an event reported as serious. Although eight (53%) experienced an event that was considered to be related to the study treatment, none of the events were reported as serious.[189]

Comparisons made to Pediatric Neuromuscular Clinical Research Cohort data

Analyses were performed to investigate the superiority of OA to the results of a natural observation studies using the historical data of a population-matched cohort[100] derived from the Pediatric Neuromuscular Clinical Research (PNCR) network. The PNCR study was a prospective cohort study which aimed to characterise the clinical features and course of SMA type 1.[100] Participants were enrolled between May 2005 and April 2009, prior to the development of the SMN-dependent treatments. Based on the limited information presented in the trial report, it is not possible to critically assess the similarity of the historical cohort to the trial cohort.

In cohort 1, all 14 (100%) participants achieved the milestone of independent sitting for at least 30 seconds at any visit up to 18 months of age, compared with none of 23 untreated patients with SMA type 1 in the PNCR cohort ($p < 0.0001$).[100, 101, 188] All 14 (100%) participants were alive and free of permanent ventilation at 14 months of age, compared with six (26%) patients in the PNCR cohort ($p < 0.0001$). Additionally, all 14 (100%) participants achieved a CHOP-INTEND score greater than 40, a threshold never achieved in untreated SMA type I patients older than six months of age ($p < 0.0001$), whose CHOP-INTEND scores instead decreased by an average 10.7 points between six and 12 months of age.

In cohort 2, all 15 (100%) participants maintained the motor milestone of independent standing for at least three seconds at any visit up to 24 months of age, compared with 19 of 81 (24%) patients with SMA in the PNCR natural history population ($p < 0.0001$).[100, 189] Additionally, 14 (93%) participants walked independently for at least five steps at any visit up to 24 months of age, compared with 17 patients (21%) in the PNCR population.

Table A5.5 Summary of SPR1NT (onasemnogene abeparvovec - presymptomatic initiation) trial baseline characteristics

Characteristic		Cohort 1 (n =14)	Cohort 2 (n =15)
Age at dosing, days	0 to 27 days	n = 11 (79%)	n = 6 (40.0%)
	28 days to 23 months	n = 3 (21.4%)	n = 9 (60.0%)
	Median	21.0 (range 8 to 34)	32.0 (range 9 to 43)
	Mean	20.6 (SD 7.87)	28.7 (SD 11.68)
Sex	Male	n = 4 (28.6%)	n = 6 (40.0%)
	Female	n = 10 (71.4%)	n = 9 (60.0%)
Ethnicity	Hispanic or Latino	n = 4 (29%)	n = 2 (13%)
	Not Hispanic or Latino	n = 10 (71%)	n = 13 (87%)
Race	Asian	n = 2 (14%)	n = 2 (13%)
	Black or African American	n = 1 (7%)	n = 1 (7%)
	White	n = 7 (50%)	n = 10 (67%)
	Other	n = 4 (29%)	n = 2 (13%)
Gestational age at birth, weeks	Mean	38.2 (SD 1.4)	38.8 (SD 1.47)
	Median	38.0 (range 36 to 41)	39.0 (range 35 to 41)
Weight at baseline, kg	Mean	3.6 (SD 0.39)	4.1 (SD 0.53)
	Median	3.7 (range 3.0 to 4.3)	4.1 (range 3.10 to 5.20)
Modality of SMA diagnosis	Prenatal testing	n = 5 (36%)	n = 1 (7%)
	Newborn screening	n = 9 (64%)	n = 13 (87%)

Characteristic		Cohort 1 (n =14)	Cohort 2 (n =15)
	Other	n = 0 (0%)	n = 1 (7%)
Age at SMA diagnosis*	Mean	7.2 (SD 4.8)	9.9 (SD 7.69)
	Median	8.0 (range 1 to 14)	8.0 (range 2 to 26)
CHOP-INTEND baseline score, median (range)	Median	49 (range 28 to 57)	NR
CMAP amplitude, median (range), mV	Median	3.9 (range 2.1 to 6.1)	4.1 (range 2.7 to 7.0)

Key: CHOP-INTEND - Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; CMAP - compound muscle action potential; SD - standard deviation; SMA – spinal muscular atrophy.

* Only calculated for participants who were diagnosed after birth. One participant in Cohort 2 was diagnosed prenatally.

Sources: Strauss et al.,[188] Strauss et al.[189]

Table A5.6 Summary of SPR1NT (onasemnogene abeparvovec - presymptomatic initiation) trial efficacy endpoint results

Endpoint		
Primary outcomes		
Cohort 1		**n = 14**
Independent sitting for at least 30 seconds	Number achieved	n = 14 (100%)
	97.5% CI	77% to 100.0%, p < 0.001*
Age when independent sitting for at least 30 seconds first achieved,	Mean	8.21 months (SD 1.756 months)
	Median	265 days (range 172 to 354)
Timing of independent sitting for at least 30 seconds demonstration†	Number achieving within normal range	n = 11 (79%)
	Number achieving but not within normal range	n = 3 (22%)
	Number not achieving	n = 0
Cohort 2		**n = 15**
Standing without support for at least 3 seconds	Number achieved	n = 15 (100%)
Age when standing without support for at least 3 seconds first achieved, months	Mean	13.5 (SD 2.18)
	Median	12.6 (range 9.5 to 18.3)
Timing of independent sitting for at least 30 seconds demonstration†	Number achieving within normal range	n = 14 (93%)
	Number achieving but not within normal range	n = 1 (7%)
	Number not achieving	n = 0
Secondary outcomes		
Cohort 1		**n = 14**
Event-free survival at 14 months	Number	n = 14 (100%)

Endpoint		
Ability to maintain weight at or above the 3rd percentile without the need for non-oral/mechanical feeding support	Number achieved	n = 13 (93%)
	Number who did not receive nutrition through mechanical support	n = 14 (100%)
	Number who maintained weight consistent with age at all visits	n = 13 (92.9%)
Cohort 2		**n = 15**
Walking without support	Number achieved	n = 14 (93%)
Age when walking without support first achieved, months	Mean	14.6 (SD 2.48)
	Median	14.1 (range 12.1 to 18.8)
Timing of milestone demonstration†	Number achieving within normal range	n = 11 (73%)
	Number achieving but not within normal range	n = 3 (20%)
	Number not achieving	n = 1 (7%)

Key: CI – confidence interval; SD - standard deviation; WHO - World Health Organization.

* A one-sided exact binomial test was used to test the null hypothesis at significance level of 0.025. The corresponding 97.5% CI was estimated by the exact method for binomial proportions

† Achievement within the WHO 99th percentile for healthy children.

Sources: Strauss et al.,[188] Strauss et al.[189]

3. Risdiplam

RAINBOWFISH[190]

Trial description

RAINBOWFISH is an ongoing international, open-label, single arm, Phase II trial that aims to evaluate the safety, pharmacokinetics, and pharmacodynamics of risdiplam in infants who initiate treatment prior to the onset of symptoms of SMA.[190] Eligible infants must have been less than or equal to six weeks of age at first dose (with minimum age of seven days at first dose) and have genetically confirmed SMA. The primary completion date was 20 February 2023 and the estimated final study completion date is 21 January 2029.

Results

As of August 2023, results for the trial have not been published in a peer-reviewed journal. However, the FDA product information reported top-line results of an interim trial analysis used to expand the product license to presymptomatic patients in the US in May 2022.[280] Reported data were limited to efficacy data for six presymptomatic patients who had been treated with risdiplam at the licensed dose for at least 12 months. Four of these patients had two copies of the *SMN2* gene while two had three copies. The median age at first dose was 35 days. All six patients were alive at 12 months without permanent ventilation. Six patients achieved sitting (100%), four patients could stand (67%) and three could walk independently (50%).

A5.2 Detailed results of trials of symptomatic initiation of treatment

1. Nusinersen

ENDEAR[191]

Trial description

ENDEAR was an international, Phase III, randomised (2:1, nusinersen:sham procedure), parallel assignment, quadruple blind (participant, care provider, investigator, and outcomes assessor) trial that aimed to evaluate the efficacy and safety trial of nusinersen in infants with SMA.[191] Eligible children must have had medically diagnosed SMA, two copies of *SMN2,* and shown signs and symptoms of SMA when aged less than 6 months old. These criteria are indicative of type I SMA.

Results

Baseline characteristics

A total of 122 participants were included in the trial. Mean age at first dose was 163 days and 181 days in the nusinersen and sham procedure arm respectively.

Efficacy endpoints

Primary endpoint:

The final analysis was based on the end-of-trial visit, conducted at least two weeks after the participant had received their most recent dose of nusinersen or undergone the sham procedure. Median (range) time on study was 280 days (range 6 to 442) days in the nusinersen group and 187 days (range 20 to 423) in the sham control group. At the final analysis, 37 (51%) participants in the nusinersen group, and no participants in the sham group had a motor milestone response as assessed by HINE-2. Considering the composite endpoint, event-free survival (event defined as death or use of permanent ventilation), there was a significant difference in favour of nusinersen (n=49 (61%) vs n=0 (0%), p = 0.005). In the nusinersen group, 16 (22%) of the infants achieved full head control, 7 (10%) were able to roll over, six (8%) were able to sit independently, and one (1%) was able to stand. In the control group, no infants achieved these milestones. The median time to death or the use of permanent assisted ventilation was 22.6 weeks in the control group and was not reached in the nusinersen group.

Secondary endpoints: There were 52 (71%) and one (3%) CHOP-INTEND responders (defined as an increase of at least four points from baseline in the CHOP-INTEND score at the end-of-trial visit) in the nusinersen group and the sham group, respectively (p < 0.001). A total of 67 (84%) and 25 (61%) participants were alive (HR = 0.37, 95% CI: 0.18 to 0.77; p = 0.004), and no use of permanent ventilation

occurred in 62 (78%) and 28 (68%) participants (HR = 0.66, 95% CI: 0.32 to 1.27; p = 0.13), in the nusinersen and sham groups, respectively.

Subgroup comparison for disease duration at study initiation

In the subgroup of participants with disease duration of less than 13.1 weeks at study initiation (median disease duration in the study), 30 (77%) participants in the nusinersen group were alive and without the use of permanent ventilation compared to seven (33%) participants in the sham group (HR: 0.24, 95% CI: 0.10 to 0.58). In the subgroup of participants with disease duration > 13.1 weeks at study initiation, 19 (46%) participants in the nusinersen group were alive and without the use of permanent ventilation compared to six (30%) participants in the sham group (HR = 0.84, 95% CI: 0.43 to 1.67). A statistical analysis to formally test if there was a statistically significant difference in treatment effects between subgroups was not conducted, but the treatment effect was numerically greater in those with a shorter disease duration compared to those with a longer disease duration.

Safety endpoints

In the nusinersen group, 77 (96%) participants experienced an adverse event, 13 (16%) experienced an adverse event leading to treatment discontinuation (all of which were classified as serious with a fatal outcome), 45 (56%) experienced a severe adverse event (defined as symptom that caused severe discomfort, incapacitation, or substantial effect on daily life), 61 (76%) experienced a serious adverse event (defined as any untoward medical occurrence that resulted in death or a risk of death, hospitalisation or prolonged hospitalisation, persistent or substantial disability or incapacity, or a congenital abnormality or birth defect), and 13 (16%) experienced a serious adverse event with a fatal outcome. In the control group, 40 (98%) participants experienced an adverse event, 16 (39%) experienced an adverse event leading to discontinuation (all of which were classified as serious with a fatal outcome), 33 (80%) experienced a severe adverse event and 39 (95%) experienced a serious adverse event. Of the adverse events identified, nine (11%) and six (15%) adverse events in the nusinersen and the control group, respectively were considered to be possibly treatment related.

CHERISH[192]

Trial description

CHERISH was an international, Phase III, randomised (2:1, nusinersen:sham), parallel assignment, quadruple blind (participant, care provider, investigator, and outcomes assessor) trial that aimed to evaluate the efficacy and safety of nusinersen in children with later-onset SMA. Eligible participants must have had medically diagnosed SMA and had symptom onset after six months of age. Additionally,

participants must have been between two and 12 years of age, have achieved the ability to sit independently but with no history of being able to walk independently, and had a HFMSE score between 10 and 54.

Results

Baseline characteristics

A total of 126 participants were included in the trial. The median ages at symptom onset were ten months and 11 months (range: six to 20 months) for the nusinersen group and sham group, respectively. The median ages at trial initiation were three years and four years (range two to nine years) for participants in the nusinersen and sham group, respectively.

Efficacy endpoints

Primary endpoint: The pre-specified interim analysis was performed when all participants had been enrolled for at least six months and at least 39 had completed their 15-month assessment. At this point, 54 participants (43%) had completed the 15-month assessment and all participants had an HFMSE score that had been obtained at six months or later. The least–squares mean change from baseline in HFMSE score was 4.0 (95% confidence interval (CI) 2.9 to 5.1) in the nusinersen group and -1.9 (95% CI -3.8 to 0) in the sham group, corresponding to a difference of 5.9 (95% CI 3.7 to 8.1; $p < 0.001$). As nusinersen was statistically superior to sham in this analysis, the trial was terminated early on recommendation from the data and safety monitoring board. Accordingly, participants who had not yet conducted their 15-month assessments completed their scheduled assessments at the end of the double blind period instead. At the final analysis, the least–squares mean was 3.9 (95% CI 3.0 to 4.9) in the nusinersen group and -1.0 (95% CI -2.5 to 0.5) in the sham group, corresponding to a difference of 4.9 (95% CI 3.2 to 6.7).

Secondary endpoints: A total of 57% of participants (95% CI 46% to 68%) in the nusinersen group and 26% of participants (95% CI 12% to 40%) in the sham group had a change in HFMSE score of three of more (which is considered to be clinically meaningful), corresponding to a difference of 30.5% (95% CI 12.7% to 48.3%; $p < 0.001$). In the nusinersen group, 13 participants (20%; 95% CI 11% to 31%) had achieved one or more new WHO motor milestones, compared to two participants (6%; 95% CI 1% to 20%) in the sham group, corresponding to a difference of 14% (95% CI -7% to 34%; $p = 0.08$). As this endpoint was not statistically significant, the remaining endpoints were deemed as exploratory due to the hierarchical testing strategy (meaning that if an endpoint did not reach significant difference, the subsequent endpoints in the pre-specified hierarchical list were considered exploratory).

Exploratory endpoints: The least-means square change from baseline in WHO motor milestones achieved was 0.2 (95% CI 0.1 to 0.3) in the nusinersen group and -0.2 (95% CI -0.4 to 0) in the sham group, corresponding to a difference of 0.4 (95% CI 0.2 to 0.7). The least-means square change from baseline in RULM scores was 4.2 (95% CI 3.4 to 5.0) in the nusinersen group and 0.5 (95% CI -0.6 to 1.6) in the sham group, corresponding to a difference of 3.7 (95% CI 2.3 to 5.0). The proportion of children who achieved the ability to stand alone or walk with assistance did not differ significantly between groups.

An analyses of the change in the HFMSE score from baseline to month 15 according to age and disease duration was presented graphically in the trial publication. Using this evidence they reported greater improvements in both younger children and in those who received treatment earlier in their disease course. The magnitude of the difference was not quantified numerically and statistical tests of significance for the subgroup analysis were not reported.

Safety endpoints

The number of serious adverse events (defined as any untoward medical occurrence that resulted in death or a risk of death, hospitalisation or prolonged hospitalisation, persistent or substantial disability or incapacitation, or a congenital anomaly or birth defect) was 14 (17%) and 12 (29%) in the nusinersen and sham group respectively. No participant in either group experienced either an adverse event leading to treatment discontinuation or leading to withdrawal from the trial. Some of the events that were reported as adverse events were noted as plausibly linked to SMA and may not have been treatment-related. Adverse events with an incidence ≥five percentage points higher in the nusinersen group than in the control group included pyrexia, headache, vomiting, back pain and epistaxis.

2. Onasemnogene abeparvovec

STR1VE[193]

Trial description

STR1VE was an open-label, single arm, Phase III trial conducted in the US that aimed to evaluate the safety and efficacy of OA in infants with genetically confirmed SMA, one or two copies of *SMN2*, and age less than six months at time of infusion. Participants could be symptomatic or presymptomatic.

Results

Baseline characteristics

A total of 22 participants were included in the trial. Although participants with one copy of *SMN2* participants and those who were presymptomatic were eligible, none

were enrolled. The mean age at baseline was 3.7 months. Follow-up time was up to 18 months.

Efficacy endpoints

Primary endpoint: Two primary endpoints were defined. A total of 13 (59%) participants were able to sit independently for at least 30 seconds at the 18 months of age study visit, with the median age of attainment at 12.6 months (interquartile range (IQR) 10.2 to 15.3). At the 14 month study visit, there were 20 (91%) participants with event-free survival, (defined as absence of death or permanent ventilation).

Secondary endpoints: Independence from ventilatory support was reported in 18 (82%) of participants. The ability to thrive was reported in nine (47%) participants.

Safety endpoints

All (100%) participants experienced an adverse event, 12 (55%) experienced a drug-related adverse event, 10 (45%) experienced a serious adverse event, and three (14%) experienced a serious drug-related adverse event. The three serious drug-related adverse events were: two participants who experienced elevated hepatic aminotransferases and one participant who experienced hydrocephalus. One death occurred due to respiratory distress, however this was considered unrelated to the treatment.

Comparisons made to PNCR

The study authors made comparisons to the results of natural observation studies using the historical data of a population-matched cohort[(100)] from the PNCR network (PNCR is described above in results of the SPR1NT trial).

In the trial participants, 59% achieved the endpoint of functional independent sitting for 30 seconds or longer at the 18 months of age study visit, compared to 0% of untreated patients in the PNCR cohort ($p < 0.0001$). Additionally, 91% of trial participants compared to 26% of participants in the PNCR cohort survived without requirement of permanent ventilation at age 14 months ($p < 0.0001$). At age 18 months, 82% of trial participants did not use ventilatory support, compared to 0% in the PNCR cohort ($p < 0.0001$). Additionally, 95% of trial participants compared to 50% of patients in the PNCR cohort were free from permanent ventilation at 10.5 months ($p < 0.0001$). While the outcomes observed in STR1VE trial are more favorable than the expected natural history of the disease observed in the untreated PNCR cohort, it is difficult to determine the robustness of the comparison because it is not possible to critically assess the similarity of the historical cohort to the trial cohort given the limited information presented in the trial report.

3. Risdiplam

FIREFISH[194, 195]

Trial description

FIREFISH is an ongoing, international, Phase II/III open-label, single arm, sequential trial that aims to assess the safety, tolerability, pharmacokinetic, pharmacodynamics, and efficacy of risdiplam in participants with type I SMA. Eligible infants were required to have genetically confirmed, symptomatic SMA with two copies of *SMN2* and be between one and seven months of age at enrolment. The trial comprised two parts: an exploratory dose finding part (part 1) and a confirmatory part (part 2). Only the results of a high dose cohort examined in part 1 of this trial are presented here. Results from a low dose cohort examined in part 1 are not reported here given the risdiplam dose administered to this group is not comparable to the licensed dose. Part two of the trial is ongoing and results have yet not been published in a peer-reviewed journal.

Results

Baseline characteristics

A total of 17 participants were included in the high dose cohort. All participants had been on treatment for 12 months at the time of the cut-off date for the analysis. Median age at enrolment was 6.3 months (range 3.3 to 6.9).

Exploratory efficacy endpoints

Post-hoc exploratory analyses of outcomes specified in part 2 of the FIREFISH trial were performed for the participants of part 1. At month 12, 16 (94%) participants achieved event-free survival. Seven participants (33%), were able to sit without support for at least five seconds, as assessed by the Bayley Scales of Infant and Toddler Development Third Edition (BSID-III). Nine participants were able to maintain upright head control at all times. A total of 10 (59%) participants achieved CHOP-INTEND scores of 40 or higher. None of the participants lost the ability to swallow, and 15 (88%) were able to feed orally. Given the exploratory nature of the analysis, the authors reported that it could not be stated with confidence that there was clinical benefit from the agent.

Safety endpoints

Safety outcomes were not reported separately for the exploratory dose finding and confirmatory study parts. All participants experienced one or more adverse events, 48% participants experienced one or more serious adverse events, and 43% experiencing an adverse event of Grade 3 to 5 (that is, requiring medical

intervention). The study did not report whether the adverse events were considered treatment related.

SUNFISH[196]

Trial description

SUNFISH is an ongoing, international, Phase II/II, randomised (2:1, risdiplam:placebo), sequential assignment trial that aims to assess the safety, tolerability, pharmacokinetic, pharmacodynamics, and efficacy in participants with type II or III SMA. The trial is comprised of two parts: an exploratory dose finding part and a confirmatory part. Eligible participants had confirmed SMA type II or III and were between 2 and 25 years of age. As part one was exploratory, and there are results available for part two, only the latter are presented here.

Results

Baseline characteristics

One hundred and twenty participants were randomised to the risdiplam group and 60 to the placebo group. The median age at trial screening was nine years in both groups. The median age at symptom onset was 14.1 months (SD 8.4) in the risdiplam group and 18.5 months (SD 21.1) in the placebo group. Most patients had type II SMA (risdiplam: 70%; placebo 73%) and three *SMN2* copy numbers (risdiplam: 89%; placebo: 83%).

Efficacy endpoints

Primary endpoint: The mean change from baseline at the 12-month assessment in the 32-item Motor Function Measure (MFM-32) total score was 1.36 (95% CI: 0.61 to 2.11) in the risdiplam group and -0.19 (95% CI: -1.22 to 0.84) in the placebo group, corresponding to a statistically significant difference of 1.55 (95% CI: 0.30 to 2.81; p=0.016).

Secondary endpoints: The number of patients with ≥3 points in MFM-32 total score was 44 (38%) in the risdiplam group, compared to 14 (24%) in the placebo group, with an OR of 2.35 (95% CI: 1.01 to 5.44).

Safety endpoints

In the risdiplam and placebo group respectively, 111 (89%) and 55 (92%) experienced an adverse event, 24 (20%) and 11 (18%) experienced a serious adverse event, and 16 (13%) and six (10%) experienced a treatment-related AE.

A5.3 Detailed results from the systematic review of Erdos et al

Nusinersen

Nineteen studies were identified for nusinersen, with these differing in their enrolment criteria, variably including differing combinations of patients with types I to IV SMA. The results are reported below as categorised within the published review which were:

- studies of SMA type I
- studies of SMA type I and II and SMA type I to III
- studies of SMA type II and III, SMA type III, and SMA type II to IV.

SMA type I:

Six prospective observational studies with 225 patients were included, five of which were single arm; one study had a cross-over design.

Mortality and discontinuation: For the five studies reporting on this outcome, loss to follow-up due to death or other reasons occurred: nine died due to massive aspiration, respiratory failure or pulmonary infection, six stopped treatment due to respiratory exacerbations related to infections, lack of motor gain, respiratory degradation, not having met improvement expectations, burden of procedure or concomitant disease, and 21 were lost to follow-up for no reported reason.

Motor endpoints: Three of three studies reported participants achieved the MCID for CHOP-INTEND scores at follow up. In one study which only reported the proportion of patients who met the MCID, one of five patients with 12 months follow-up, one of seven patients with 18 months follow-up, and two of three patients with 24 months follow-up reached the MCID for HINE-2, while in the other study 93% of participants were classified as HINE-2 responders with 100% of participants achieving the MCID threshold.

Safety: Drug-related adverse events were reported in two studies, with one reporting no events, and one reporting that 14% of participants experienced them. In two studies, procedure-related adverse events were reported, with post-lumbar puncture syndrome, unsealed puncture site with temporary cerebrospinal fluid leakage and post-puncture headache occurring in 15%, in 7% and in 2% of patients, respectively. One study reported that serious adverse events occurred in 64% of participants, however it was not clear whether these were drug or procedure related.

SMA type I and II and SMA type I to III:

Five studies were identified; four which enrolled participants with SMA types I to III and one which enrolled participants with SMA types I and II. One study was retrospective and the other four were prospective observational single arm studies. Overall, there were 66 participants with SMA type I, 161 with SMA type II, and 33 with SMA type III.

Mortality and discontinuation: For the five studies reporting on this outcome, loss to follow-up due death or other reasons occurred: eight died, six stopped treatment due to tolerability issues with nusinersen or with the functional assessment at follow-up, one was excluded due to a spinal surgery potentially impacting the results, and loss to follow-up for no reported reason.

Motor endpoints: Two of four studies reported an improvement from baseline to last follow-up that exceeded the MCID for CHOP-INTEND scores. Two studies reported a combined CHOP-INTEND and HFMSE scales with one reporting that a third of participants reached the MCID and two thirds remained stable, and the other studied reported a significant improvement after 14 months of treatments in participants with SMA types I and II, with trends towards improvement observed in participants with SMA type III. HINE-2 scores were reported for one study, with improvements in the number of SMA type I participants reaching the MCID threshold, but only 44% reached the MCID threshold in the combination analysis for SMA type I and II participants. In one study reporting HFMSE scores at 12 months follow-up, the MCID was reached for SMA type III participants, but not for SMA type II participants. Two studies reported RULM scores, with the MCID being reaching in only one study and only in participants with type II SMA. The 6MWT was used in one study, no improvements from baseline were noted.

Safety: In 20 to 40% of participants, adverse events occurred, mainly related to the lumbar puncture (headache, post lumbar puncture syndrome, nausea and vomiting). Three studies reported no serious adverse events.

SMA type II and III, SMA type III, and SMA type II to IV:

Five studies included participants with SMA types II and III, and one each for participants with SMA type III, SMA types III and IV, and SMA types II to IV. Five studies were prospective observational single arm studies and four were a retrospective study design of which two included a historical control group. Overall, there were 93 participants with SMA type II, 245 with SMA type III and three participants with SMA type IV.

Mortality and discontinuation: Loss to follow-up due to death or other reasons occurred in 14 participants: one died due to respiratory failure, five stopped treatment due to lack of perceived benefit and poor tolerability of lumbar puncture, two patients withdrew because of adverse drug reactions, two withdrew for no reported reason, and four were lost to follow-up for no reported reason.

Motor endpoints: One study reported CHOP-INTEND scores in participants who were unable to sit at baseline. While there was improvement in the scores, the changes were below the MCID threshold. HFMSE scores were reported in eight studies, with improvements above the MCID reported in three studies and some improvements

that were below the MCID reported in five studies. In one of the latter studies, improvements were reported for subgroups by SMA type, with MCID threshold obtained in participants with SMA type II and a decrease of one point in participants with SMA type III. Six studies reported RULM scores, with one study reporting improvements that were below the MCID and one reporting improvements that met the MCID threshold. Follow-up data for the 6MWT was reported in four studies, with two studies reporting an increase that exceeded the MCID.

Safety: One study reported that most non-serious adverse events were not related to the drug. Two studies reported that 47% of participants experienced drug-related adverse events and 23% experienced procedure-related adverse events. Two studies reported 13 drug-related adverse events and 255 adverse events related to the intrathecal injection procedure, including post-puncture headaches and lower back pain, (the percentage of participants was not reported). One study reported procedure-related adverse events in 41% of participants. Four studies reported on serious adverse events, with one study reporting that there was two events.

Onasemnogene abeparvovec

One study was identified which included 24-month follow up for 12 participants with SMA type I. Subgroups in the intervention group were: early dosing/low motor group (less than three months of age at dosing and baseline CHOP-INTEND score < 20; mean age at dosing 1.8 months (SD 0.76)), early dosing/high motor group (less than three months of age at dosing and baseline CHOP-INTEND score ≥20; mean age at dosing 1.8 months (SD 0.85)), and late dosing group (three months of age or older at dosing; mean age at dosing: 5.1 months (SD 1.56)).

Mortality and discontinuation: There were no deaths or loss to follow-up.

Motor endpoints: Relative to baseline CHOP-INTEND scores, all the subgroups in the study (early dosing/low motor group, early dosing/high motor group, and late dosing group) obtained the MCID threshold. The biggest improvement was observed in the early dosing/low motor group, while the smallest improvement was observed in the early dosing/high motor group. All but one participant (a participant from the late dosing group) was able to sit without support for five seconds, and nine were able to sit for at least 30 seconds (all the participants from the two early dosing groups). Two were able to walk alone (both from the early dose/high motor group).

Safety: There were 275 adverse events, of which 53 (19%) were serious events, with two of these associated with the treatment.

Combination therapy of nusinersen and onasemnogene abeparvovec

Two single arm observational studies were identified, both of which included only patients with SMA type I. One study, which was retrospective and had follow-up

time of 19.2 months, included four participants who were on nusinersen prior to OA, three of which continued nusinersen with OA, and one patient who received nusinersen only after OA administration. The other study, which was a long-term follow up study of a Phase I trial of OA (START), had a follow up time of 5.2 years. Of 13 participants enrolled in the study, seven were receiving concomitant nusinersen to attempt to improve benefits, not because of a loss of motor function or regression. This study however did not report the results separately for the group who received nusinersen as concomitant therapy and for the group who received OA only. Therefore, only results from the study reporting results for combination therapy separately are included below.

Mortality and discontinuation: There were no deaths reported.

Motor endpoints: CHOP-INTEND and HINE-2 improvements were reported which crossed the MCID threshold in all participants with data available (five participants with CHOP-INTEND scores and two with HINE-2 scores). The same study reported that 40% of patients were able to sit independently and stand with support, 40% were able to sit independently, 20% could only control their head and kick. However, the baseline motor functions were not reported.

Safety: Liver enzyme elevation and liver injury were reported, which were drug-related caused by OA. There was no evidence of drug-related adverse events caused by nusinersen.

Appendix Chapter 6

Table A6.1 Characteristics of the screening and diagnostic testing strategies

Author Country	Screening uptake (%)	Test accuracy	Screening platform	Adjusted screening test cost‡	Confirmatory test	Adjusted cost of confirmatory test†
INESSS 2021[14]	97.6%	False negatives: 2 to 5%	First line - detection of *SMN1* deletion using DNA amplification. The same equipment and screening kit can be used to detect SCID and XLA.	€7.26	Second line - number of *SMN2* copies	Unclear
Jalali 2020[208]	NR	NR	Costs of screening (e.g., staff and instrumentation), were not accounted for because utilisation of these resources is likely invariant to the inclusion of SMA	€2.51	NR	NR
Shih 2021§[207, 209]	NR	False negatives: 0.00000576%	Real-time PCR for homozygous *SMN1* exon 7 deletion. Multiplex assay for SMA and SCID.	€3.00	Confirm *SMN1* deletion results by MPLA. *SMN2* copy number by ddPCR	NR
Velikanova 2022[205]	> 99%	Sensitivity: 100%‡ Specificity: 100%	qPCR for homozygous *SMN1* deletion	€5.25	ddPCR or MLPA	€1,697
Weidlich 2023[206]	NR	NR	qPCR for homozygous *SMN1* deletion	€5.40	Genetic sequencing and MPLA	€1,428

Key: DNA - Deoxyribonucleic acid; ddPCR - Droplet digital polymerase chain reaction; MLPA - Multiplex ligation-dependent probe amplification; NR – not reported; qPCR – real time polymerase chain reaction; SCID – severe combined immunodeficiency; *SMN1/SMN2* - survival motor neuron gene 1 / survival motor neuron gene 2; XLA - X-linked agammaglobulinemia.

† Costs have been adjusted based on national consumer price indices and purchasing power parities in accordance with national HTA guidelines.

‡ Newborn bloodspot screening does not identify *SMN1* compound heterozygous variants; this patient group was assumed to be diagnosed clinically. In the base case analysis, the sensitivity and specificity of the newborn bloodspot screening test for SMA were assumed to be 100%. In scenario analysis, the impact on the ICER if 5% of SMA cases have a *SMN1* compound heterozygous variant was investigated.

§ Based on methods reported in a companion manuscript.[209, 281]

Table A6.2 Results of cost-effectiveness analyses

Author (year)	Country	Strategy	Adjusted ICER
INESSS 2020[14]	Canada	Screening for SMA versus clinical presentation	€614,129 per additional case detected
			€133,248 per case detected
			€22,296 per month of diagnostic delay avoided
Jalali 2020[208]	United States	Newborn bloodspot screening and treatment of infantile-onset SMA with nusinersen versus nusinersen treatment without universal screening (ENDEAR trial)	€206,653 per LYG
		NBS and treatment of infantile-onset SMA with nusinersen, versus nusinersen treatment without universal screening (preliminary data from NURTURE trial)	€224,699 per LYG
Velikanova 2022[205]	The Netherlands	Newborn bloodspot screening for SMA and subsequent treatment versus no screening (diagnosis and treatment after symptomatic presentation)	Dominant
Weidlich 2023[206]	England and Wales	Newborn bloodspot screening for 5q SMA versus (pre-symptomatic or symptomatic identification and treatment) no screening (symptomatic presentation and treatment)	Dominant

Key: ICER – incremental cost effectiveness ratio; LYG – life year gained; SMA – spinal muscular atrophy.

Table A6.3 Results for additional base case comparisons

Author (year)	Country	Strategy	Time horizon	Adjusted ICER† (per LYG)	Adjusted ICER† (per QALY)
Jalali 2020[208]	United States	**Base case analysis**			
		Newborn bloodspot screening without nusinersen treatment versus no screening and no treatment (ENDEAR trial data)	Lifetime	Dominated‡	Dominated‡
		Nusinersen without screening versus no screening and no treatment (ENDEAR trial data)		€438,040	€449,788
		Newborn bloodspot screening with nusinersen treatment versus nusinersen treatment without screening (ENDEAR trial data)		€167,010	€171,871
		Newborn bloodspot screening with nusinersen treatment versus nusinersen treatment without screening (NURTURE trial data)		€219,572	€225,535
		Adjusted for early and late treatment effects			
		Newborn bloodspot screening without nusinersen treatment versus no screening and no treatment (ENDEAR trial data)	Lifetime	Dominated‡	Dominated‡
		Nusinersen without screening versus no screening and no treatment (ENDEAR trial data)		€484,036	€495,468
		Newborn bloodspot screening with nusinersen treatment versus nusinersen treatment without screening		€206,653	€213,206

Author (year)	Country	Strategy	Time horizon	Adjusted ICER† (per LYG)	Adjusted ICER† (per QALY)
		(ENDEAR trial data)			
		Newborn bloodspot screening with nusinersen treatment versus nusinersen treatment without screening (NURTURE trial data)		€224,699	€231,004
Shih 2021[207]	Australia (New South Wales/Australian Capital Territory NBS pilot)	Newborn bloodspot screening and nusinersen treatment versus newborn bloodspot screening and gene therapy	5 years	NR	Dominant§
		and nusinersen treatment versus no newborn bloodspot screening and nusinersen treatment		NR	€296,348
		Newborn bloodspot screening and nusinersen treatment versus no newborn bloodspot screening and supportive care		NR	€742,071
		Newborn bloodspot screening and gene therapy versus no newborn bloodspot screening and nusinersen treatment		NR	€428,325
		Newborn bloodspot screening and gene therapy versus no newborn bloodspot screening and supportive care		NR	€815,858
		No Newborn bloodspot screening and nusinersen treatment versus supportive care		NR	€1,307,172
		Newborn bloodspot screening and nusinersen treatment versus	Lifetime	NR	Dominated‡§

Author (year)	Country	Strategy	Time horizon	Adjusted ICER† (per LYG)	Adjusted ICER† (per QALY)
		Newborn bloodspot screening and gene therapy			
		Newborn bloodspot screening and nusinersen treatment versus no newborn bloodspot screening and nusinersen treatment		NR	€307,746
		Newborn bloodspot screening and nusinersen treatment versus no newborn bloodspot screening and supportive care		NR	€346,140
		Newborn bloodspot screening and gene therapy versus no newborn bloodspot screening and nusinersen treatment		NR	Dominant§
		Newborn bloodspot screening and gene therapy versus no newborn bloodspot screening and supportive care		NR	€129,577
		No Newborn bloodspot screening and nusinersen treatment vs supportive care		NR	€423,526

Key: ICER – incremental cost effectiveness analysis; LYG – life year gained; NR – not reported; QALY – quality-adjusted life year

† Adjusted ICER is defined as inflation of a context-specific ICER using country-specific consumer price indices (CPI) to a common cost year (2020), prior to conversion to a common currency (Irish Euro) using purchasing power parities (PPPs). PPPs are indicators of price level differences between countries. Even in countries using a common currency (e.g., Euro), differences in local economies influence the price of products.

‡ The intervention is more costly and results in poorer health outcomes.

§ Shih et al. assume equivalent clinical outcomes for nusinersen and gene therapy due to the absence of evidence for gene therapy at the time of analysis. Comparisons differ in terms of cost only.[207]

Table A6.4 Results of cost effectiveness analyses in the original and Irish context

Author (year)	Country	Base case strategy[†]	Original context			Irish context	
			Unadjusted ICER (per QALY)	WTP threshold (per QALY)	Interpretation	Adjusted ICER[‡§] (€/QALY or €/case detected)	Interpretation at WTP thresholds of €20,000 and €45,000 per QALY
INESSS 2021[(14)]	Canada	Newborn bloodspot screening for SMA versus clinical identification (cost per additional case)	$931,000 CAD	NA	NA	€614,129	NA
		Newborn bloodspot screening for SMA versus clinical identification (cost per additional case detected)	$202,000 CAD	NA	NA	€133,248	NA
		Newborn bloodspot screening for SMA versus clinical identification (cost per month of diagnostic delay avoided)	$33,800 CAD	NA	NA	€22,296	NA
Jalali 2020[(208)]	US	Universal screening and treatment of infantile-onset SMA with periodic injections of nusinersen versus nusinersen treatment without universal screening (adjusted for early and late treatment effects; ENDEAR trial)	$247,492 USD	US $50,000 and $500,000[††]	Cost effective or not cost effective, depending on the WTP threshold	€213,206	Not cost effective

Author (year)	Country	Base case strategy[†]	Original context			Irish context	
			Unadjusted ICER (per QALY)	WTP threshold (per QALY)	Interpretation	Adjusted ICER[‡§] (€/QALY or €/case detected)	Interpretation at WTP thresholds of €20,000 and €45,000 per QALY
		Universal screening and treatment of infantile-onset SMA with periodic injections of nusinersen versus nusinersen treatment without universal screening (adjusted for early and late treatment effects; NURTURE trial)	$268,152 USD	US $50,000 and $500,000[††]	Cost effective or not cost effective, depending on the WTP threshold	€231,004	Not cost effective
Shih 2021[(207)]	Australia (New South Wales/Australian Capital Territory NBS pilot)	Newborn bloodspot screening for SMA and early treatment with nusinersen versus nusinersen treatment without screening (primary comparator)	$513,000 AUD	AUS $50,000	Not cost effective	€307,746	Not cost effective
		Newborn bloodspot screening for SMA and early treatment with OA versus nusinersen treatment without screening (primary comparator)	Dominant	AUS $50,000	Cost saving	Dominant	Cost saving
Velikanova 2022[(205)]	The Netherlands	Newborn bloodspot screening for SMA and subsequent treatment	Dominant	€20,000	Cost saving	Dominant	Cost saving

Author (year)	Country	Base case strategy[†]	Original context			Irish context	
			Unadjusted ICER (per QALY)	WTP threshold (per QALY)	Interpretation	Adjusted ICER[‡§] (€/QALY or €/case detected)	Interpretation at WTP thresholds of €20,000 and €45,000 per QALY
		versus no screening (diagnosis and treatment after symptomatic presentation)					
Weidlich 2023[(206)]	England and Wales	Newborn bloodspot screening for 5q spinal muscular atrophy versus (pre-symptomatic or symptomatic identification and treatment) no screening (symptomatic presentation and treatment)	Dominant	GBP £20,000, £30,000, and £100,000	Cost saving	Dominant	Cost saving

Key: AUD – Australian dollars; CAD – Canadian dollars; GBP – Great British pound (Pound sterling); ICER – incremental cost effectiveness ratio; NA – not applicable; QALY – quality-adjusted life year; SMA – spinal muscular atrophy; USD – United States dollars; WTP – willingness to pay.

[†] Where studies presented multiple combinations of screening and alternative treatment strategies in the base case analysis, only strategies most relevant to the current treatment landscape are presented. Comparisons with historical management strategies (clinical presentation and supportive care prior to the availability of pharmacological agents irrespective of SMA genotype or phenotype) are not shown.

[‡] Where multiple time horizons were used, results for the longest time horizon are presented.

[§] Adjusted ICER is defined as inflation of a context-specific ICER using country-specific consumer price indices (CPI) to a common cost year (2020), prior to conversion to a common currency (Irish Euro) using purchasing power parities (PPPs). PPPs are indicators of price level differences between countries. Even in countries using a common currency (e.g., Euro), differences in local economies influence the price of products.

[††] WTP threshold for evaluating ultra-rare diseases only.

Appendix Chapter 7

Table A7.1 Key assumptions

Assumption	Rationale
Programme requirements	
The uptake rate will reflect the current uptake rate for NBS screening.	Expert opinion.[86]
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.
No additional funding is required to update NNBSP material and disseminate changes to practice.	A previous budget impact analysis of the addition of SCID to the NNBSP estimated the cost of updating educational resources for parents or guardians and healthcare professionals including information leaflets, an eLearning module, delivery of information sessions, and updates to policies, procedures, protocols and guidelines. In the event that screening for SMA is approved for addition to the NNBSP, implementation of screening for SCID and SMA would occur concurrently given that both conditions use the same testing platform. The cost of updates to educational materials previously estimated for the addition of SCID screening to the NNBSP was assumed to cover the cost of all changes required at the time of implementation.
Screening and confirmatory testing	
Approximately 58,000 infants would be eligible for screening per annum.	It was estimated that approximately 58,000 newborns annually would be eligible for screening based on the average projected births between 2024 and 2033.[236] 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 (M1F2). Variation in annual births between Dublin outflow and inflow scenarios is typically less than three births per annum during the years considered (2024 to 2033).

Assumption	Rationale
	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.[282]
5% of cases with SMA are not identified by screening due to limitations of the testing methodology.	Cases with compound heterozygous variations are not detected by this screening method. As described in chapter 3, it is estimated that this accounts for 2% to 5% of all cases of SMA.
All patients with a homozygous deletion of SMN1, irrespective of *SMN2* copy number, would be considered screen positive cases.	As highlighted in chapters 2 (section 2.4) and 4 (section 4.3.3), the definition of a positive screening test varies internationally, which is typically linked to reimbursement criteria in that jurisdiction. In the Irish context, the parent(s) or legal guardian(s) of infants of infants participating in the NNBSP are only contacted if the infant has a positive screening test result for any one of the nine conditions currently screened for (that is, negative results are not communicated to parent(s) and legal guardian(s)).[232] For the purposes of this analysis, as a conservative approach, it was assumed that the parent(s) or legal guardian(s) of infants with homozygous *SMN1* deletion would be informed, irrespective of *SMN2* copy number, to facilitate access to treatment or monitoring, as appropriate. Of note, given that 85% of patients would have three or fewer copies of *SMN2,* based on the international epidemiological literature, changes in the definition of screen positivity to include or exclude cases with higher *SMN2* copy numbers would be unlikely to have significant short-term budgetary consequences. Potential ethical consequence of the definition of screen positive cases adopted are discussed in chapter 8.
Confirmatory testing would take place at the Molecular Genetics Laboratory at CHI Crumlin.	In the base case analysis, it was assumed that diagnostic testing would be conducted at the Molecular Genetics Laboratory at CHI Crumlin given that the laboratory has the equipment required, skilled staff and sufficient capacity to process positive screening test results based on estimates of screening test outcomes from the international literature.

Assumption	Rationale
Confirmatory testing would be carried out using the original dried bloodspot sample.	As part of the systematic review of clinical effectiveness to synthesise the evidence relating to the approach to and outcomes of newborn bloodspot screening programmes for SMA (chapter 4), it was identified that approximately half of existing programmes use a two tier testing strategy to diagnose SMA, whereby screening and confirmatory testing are conducted on the original dried bloodspot sample. Based on consultation with the NNBSP and the NNBSL, it was noted that this approach would be preferred in practice, if feasible, for the following reasons: ▪ the potential for operational efficiencies at a laboratory level including increased test turnaround times ▪ reduced healthcare resource use related to requirements for additional outpatient appointments in circumstances where a blood draw is needed to carry out confirmatory testing ▪ elimination of the risk of unnecessary stress and anxiety for families associated with communication of false positive results of screening. For the purposes of the budget impact analysis, it was assumed that confirmatory testing would be conducted using the original dried bloodspot sample. In practice, the feasibility of this would be dependent on the outcomes of verification of the testing method.
There is sufficient capacity within existing resources to undertake cascade testing of family members, where indicated.	Once a patient with SMA is identified, through clinical presentation or screening, cascade testing may be offered to parents of the affected infant to determine carrier status. Where clinically indicated, cascade testing of siblings may also be performed (see section 7.2.2). Cascade testing of family members of cases presenting symptomatically is currently conducted at the Molecular Genetics Laboratory at CHI Crumlin. In the event that screening for SMA is introduced, based on consultation with the NNBSP, it is anticipated that there would be sufficient capacity in the Molecular Genetics Laboratory to conduct cascade testing in addition to the capacity required for second-tier testing of screen positive cases. Therefore, for the purposes of the budget impact analysis, it was assumed there would be no additional costs associated with cascade testing. It is likely that the vast majority of those offered cascade testing following a positive screening test result would be offered testing at some point in their lives in the absence of screening. Therefore, screening would likely not result in absolute increase in the demand for cascade testing, but would change the timing of such testing.

Assumption	Rationale
	Demand for cascade testing is challenging to predict as it is highly dependent on the number of siblings in a family, as well as the age and symptom status of those siblings. Furthermore, not all those offered cascade testing may wish to access testing due to the known variable risk-benefit balance.
No additional resources (staff or equipment) would be required to process positive screening test results at the Molecular Genetics Laboratory at CHI Crumlin.	Based on consultation with representation from the Molecular Genetics Laboratory at CHI Crumlin, it was assumed that diagnostic testing could be completed within existing capacity. However, this assumption is dependent on the false positive rate from screening being close to that observed in international practice based on a systematic review of existing SMA screening programmes (chapter 4, see section 4.3.5). Based on the maximum observed false positive rate of 0.008% (n = 14 studies; n =1 excluded due to evidence of heparin contamination), in the Irish context, the upper bound for false positive screening test results was estimated to be 5 cases. However, if a decision were made to implement screening for SMA, the outcomes of screening in the Irish context would be dependent on the results of local verification of the testing method. A higher rate of false positive results than the assumed rate of 0.008% would create a burden on resources at the Molecular Genetics Laboratory at CHI Crumlin. If requirements for diagnostic testing exceed available capacity at the Molecular Genetics Laboratory at CHI Crumlin, additional equipment would be required to establish second tier testing at the NNBSL (see section 7.2.2).
Treatment	
Patients treated following clinical presentation present slowly over time.	As highlighted in chapter 3, the age at clinical presentation with SMA can be wide ranging depending on the disease type. For example, patients with type III SMA may present any time between 18 months and eighteen years of age. The minimum and maximum age at symptom onset (screening cohort) and diagnosis (standard care cohort) as reported by an Italian study were used to inform the range of possible values for timing of treatment initiation for each SMA subtype.[96] Incident cases were equally distributed between the minimum and maximum time of symptom onset or diagnosis. In the base case, in the screening cohort, only patients with four or more copies of *SMN2* were assumed to present clinically. Cases with fewer than three *SMN2* copies would be treated presymptomatically.
It was assumed that all patients eligible for treatment with OA according to current	Onasemnogene abeparvovec uses the AAV9 vector to deliver the *SMN1* gene. Neutralizing antibodies caused by previous natural exposure to wild-type adeno-associated viruses, or placental transfer or maternal antibodies, may

Assumption	Rationale
reimbursement criteria would receive OA (see chapter 5, section 5.3).	impair the efficiency of AAV-mediated gene transfer, and thus may reduce the therapeutic benefit of OA. As a result, an AAV9-binding antibody titre of > 1:50 is considered an exclusion criterion for treatment with OA.[31] Available evidence suggests that the percentage of patients with exclusionary anti-AAV9 antibody titres is low.[31, 283] Thus, most infants with SMA type I or ≤ 3 *SMN2* copies should be able to receive OA.
Testing for anti-AAV9 antibodies would continue to be delivered by an external provider in the Netherlands.	In the context of the small annual birth cohort and low SMA incidence, there may be insufficient testing volumes in Ireland to quality assure testing for anti-AAV-9 titres. Centralised testing for elevated anti-AAV-9 titres is currently conducted in a single laboratory in the Netherlands. In the event that screening for SMA is introduced, it is anticipated that testing would continue to be delivered at this site. It is anticipated that there would be no additional cost.
Patients treated with risdiplam would be monitored at the same frequency as patients who are treated with OA.	For the purposes of this analysis, it was assumed that the clinical pathway would be similar to that of patients managed with OA. Patients would be monitored as an outpatient every one to two weeks for the first two to three months (range four to 12 appointments in year one of treatment). Thereafter, patients would require two to three outpatient appointments per annum for monitoring of long-term treatment outcomes.
Patients treated with OA do not transition to another disease modifying therapy (nusinersen or risdiplam) in the screening or standard care cohorts.	Currently the evidence base at point of regulatory approval mainly considers available disease modifying therapies as standalone treatments.[253] Although clinical trials of concomitant therapy are underway (for example, NCT04488133), at the time of analysis, there was no published evidence to suggest that combination therapy is more effective than any single treatment.[254]
Of patients with types II or III SMA, 50% will be treated with nusinersen and 50% will be treated with risdiplam.	As noted in chapter 5, risdiplam was approved for reimbursement in September 2023, making it challenging to predict future prescribing patterns. For the purposes of this analysis, an equal market share for nusinersen and risdiplam was assumed in the base case analysis. In clinical practice the treatment strategy would be decided on an individual patient basis with consideration to factors such as the available clinical effectiveness and safety data, experience at the treating centre, and patient preferences.

Key: AAV- 9 - adeno-associated virus 9; CHI - Children's Health Ireland; CSO – central statistics office; HSE – Health Service Executive; NBS – newborn bloodspot screening; NNBSL - National Newborn Bloodspot Screening Laboratory; OA – onasemnogene abeparvovec; SCID – severe combined immunodeficiency disease; SMA – spinal muscular atrophy; *SMN* - survival motor neuron.

Published by the Health Information and Quality Authority (HIQA).

For further information please contact:

Health Information and Quality Authority

George's Court

George's Lane

Smithfield

Dublin 7

D07 E98Y

+353 (0)1 8147400

info@hiqa.ie

www.hiqa.ie