Health Information and Quality Authority

An tÚdarás Um Fhaisnéis agus Cáilíocht Sláinte

Protocol for the Health Technology Assessment of the addition of spinal muscular atrophy (SMA) to the National Newborn Bloodspot Screening Programme

20 July 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.

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Background to the HIQA/NSAC work programme

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

1 Introduction

1.1 Background

Newborn bloodspot screening commenced in Ireland in 1966 with the development of a national screening programme for phenylketonuria (PKU).[1] Currently, in Ireland, the National Newborn Bloodspot Screening Programme (NNBSP) screens for nine conditions. In January 2023, following a HIQA HTA and recommendation from NSAC, the Minister for Health approved the addition of severe combined immunodeficiency (SCID) to the programme. Participation in the NBS programme in Ireland is high, with an estimated uptake of 99.9%.[2] Each year, approximately 60,000 infants are born in Ireland, and the NNBSP identifies approximately 110 babies in Ireland with one of the conditions screened for through the programme.

Spinal muscular atrophy (SMA) is an autosomal recessive neuromuscular condition, the severity of which varies according to the underlying genotype. The most severe forms are associated with significant morbidity and mortality; however, there are now effective treatments that can modify the course of the condition.[3] In December 2022, at the request of NSAC, HIQA agreed to undertake a HTA of the addition of SMA to the NNBSP. The present document describes the evidence synthesis approach that will be adopted in the HTA.

1.2 Condition and screening technology

SMA is an autosomal recessive neuromuscular condition caused by mutation in genes that code for the survival motor neuron (SMN) protein.[4] 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 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 irreversible muscle weakness.[3, 5, 6] Most of the SMN protein is a product of the *survival of motor neuron 1* (*SMN1*) gene on the long arm ('q') of chromosome 5. The *SMN2* gene also

encodes the SMN protein; however, only around 10% of the gene-product is a full length SMN protein.[7]

Most cases (95%) of SMA are caused by a homozygous (that is, involving both alleles) deletion of exon 7 of the *SMN1* gene. Less frequently (5% of cases), SMA results from a deletion of exon 7 on one of the copies of the *SMN1* gene alongside a smaller, more specific mutation (point mutation) on the other copy of the gene.[8] 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. Mutations in other genes can also be causative of SMA, resulting in a range of conditions known as non-5q-SMA. While there is clinical overlap between 5q-SMA and non-5q-SMA, an important distinction is that non-5q-SMA cannot be detected through screening for deletion of the *SMN1* gene. It is therefore considered out of scope for this HTA. Within the context of this protocol and the HTA, 5q-SMA will henceforth be referred to simply as SMA.

As previously noted, the SMN2 gene also produces SMN protein, however only 10% of the gene product is functional SMN. [7] Severity of SMA is modulated by the number of copies of *SMN2* gene, with more copies generally resulting in less severe disease. The condition has traditionally been classified into five subtypes, Types 0 to IV, based on symptom severity and motor milestones met.

SMA can be detected through newborn screening on a dried bloodspot (DBS).[7] Screening is performed on isolated DNA, most commonly using real-time polymerase chain reaction (PCR), in order to detect the homozygous deletion of exon 7 on the *SMN1* gene. Once detected, diagnostic testing to confirm SMA is undertaken as well as evaluation of the number of SMN2 copies. Of note, as the initial screening using a dried bloodspot sample aims to detect the homozygous deletion of exon 7 on the *SMN1* gene, those cases (approximately 5%) that arise due to a single allelic deletion and a point mutation on the other allele will not be detected by this method.

1.3 Evidence synthesis approach

HTA is a multidisciplinary process that summarises information about the medical, social, economic and ethical issues related to the use of a health technology and does so in a systematic, transparent, unbiased, and robust manner. HTAs are designed to inform safe and effective health policies that are both patient-focused and achieve the best value.

The HTAs conducted by HIQA's HTA Directorate follow the HTA Core Model® proposed by the European Network for Health Technology Assessment (EUnetHTA).[9] As per the Core Model, HTAs conducted by HIQA's HTA Directorate commonly include the following domains:

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

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

1.4 Aims and objectives

In the subsequent sections of this protocol, the scope and methods of the HTA are described according to the HTA domains that will be assessed. The objectives of this HTA are as follows:

- describe the existing and proposed diagnostic and treatment pathway for SMA in Ireland
- conduct a review on the international practice of the use of newborn screening for SMA
- describe the epidemiology and burden of disease of SMA.
- perform a review of the test accuracy of newborn 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 screening for SMA
- consider any wider organisational, ethical or societal implications that newborn screening for SMA may have for patients, families, the general public or the healthcare system in Ireland.

Additionally, given the recent recommendation for the addition of SCID to the NNBSP and that these conditions may be screened using the same technology, the HTA will consider any impact that screening for SMA may have on screening for SCID (for example, potential for shared resources).

The NSAC has established a list of 20 criteria for appraising the viability, effectiveness and appropriateness of a national population-based screening programme.[10] These 20 criteria are grouped under five categories, as follows:

- the condition
- the screening method
- the intervention
- the screening programme

- implementation.

The HIQA HTA team performed a mapping exercise to identify how the typical domains of a HTA, as per the HTA Core Model®,[9] relate to the NSAC criteria. This mapping exercise aimed to clarify the extent to which the output of a HTA might address the NSAC criteria, and which section of the HTA addresses which criterion/criteria. A full list of the NSAC criteria and their corresponding HTA domains, as identified by HIQA, is presented in Appendix 1.

2 Description of technology

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

- the current diagnostic and treatment pathway for children with SMA (including follow-up) in Ireland
- the method of screening for SMA in newborns (including diagnostic follow-up to a positive screen)
- international practice in the use of screening for SMA in newborns.

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

2.1 Current diagnostic and treatment pathways

This section will comprise an overview of the diagnostic and treatment pathway. It will be informed by a review of international clinical guidelines, publicly available literature, consideration of current Irish pathways, and by expert clinical opinion.

For those diagnosed with SMA, treatment is guided by their underlying subtype (Type 0, I, II, III, or IV), functional status, and symptoms. This section will provide a brief overview of the specific treatment options which primarily include disease-modifying drugs that increase functional SMN protein production, known as SMN pathway-dependent drugs.[5, 6] The clinical effectiveness of specific treatments reimbursed for use by the HSE will be considered in section 5.3.

A range of pharmaceutical and non-pharmaceutical interventions are used to support the symptomatic management of SMA. This section will also provide a brief overview of the range of supportive treatments for common issues (for example, bulbar dysfunction leading to poor weight gain, bowel dysfunction, respiratory insufficiency) in children with SMA. While these will be mentioned, they will not be described in detail.

2.2 Screening for SMA in newborns

The method of screening for SMA in newborns will be described in detail alongside the process for confirmatory testing and diagnosis. This description will be informed by review of publicly available literature and expert opinion, as appropriate.

2.3 International practice

An overview of international practice, describing the countries that currently have newborn bloodspot screening programmes in place for SMA and the screening tests used, will be provided. The overview will be informed by reviewing grey literature sources (for example, national public health organisations, and the websites of governmental departments and relevant agencies), and recent, peer-reviewed literature.[5, 11-13] The overview will focus on countries of most relevance to Ireland, including:

- countries in the European Economic Area
- United Kingdom
- United States
- Canada
- Australia
- New Zealand.

3 Epidemiology

The purpose of this chapter is to provide an overview of the epidemiology of SMA. The specific aims of this chapter will be to describe:

- SMA and its subtypes
- the aetiology, symptoms and natural progression of SMA and its subtypes
- the burden (incidence, prevalence, morbidity, and mortality) of SMA.

The known subtypes of SMA will be presented according to their description within the clinical literature and the Irish context where possible. An overview of the literature and clinical data on the genetic patterns of inheritance, symptom presentation and natural history of SMA and subtypes of SMA will also be presented.

Where available, national data and relevant international data on the morbidity and mortality associated with SMA will be presented.

4 Overview of treatments

This section aims to describe the clinical effectiveness and safety of the disease modifying (SMN pathway-dependent) EMA-approved treatments for SMA.

Treatment for SMA may include multidisciplinary management of respiratory, nutritional and gastroenterological, orthopaedic, and psychosocial issues.[8] Historically, SMA was managed symptomatically, but over the last several years, disease-modifying drug treatments have emerged which act to modify the levels of SMN protein (known as SMN pathway-dependent treatments). The three EMA-authorised SMN pathway-dependent drugs are nusinersen (authorised in 2017), onasemnogene abeparvovec (authorised in 2020), and risdiplam (authorised in 2021).[14-16]

This section will aim to describe the mechanism of action, route of administration, indications, reimbursement status, pivotal trials informing EMA reimbursement, and clinical trials of presymptomatic treatment initiation. A de novo systematic review will not be undertaken as the effectiveness of these treatments has been extensively described in recent literature with consistency of findings between studies. A narrative summary will be provided of data obtained from trial registries and publications of the trials for pre symptomatic initiation, and an overview will be provided of literature identified for the symptomatic initiation of the drugs.

5 Clinical effectiveness of screening

Evidence underpinning the effectiveness of the screening method is central to decision-making regarding the expansion of newborn bloodspot screening. Accordingly, this HTA chapter aims to describe the clinical effectiveness of newborn screening for SMA.

A systematic review will be undertaken to identify, appraise and synthesise relevant international literature in relation to the effectiveness of newborn bloodspot screening for SMA. The proposed review question and methods are outlined below.

5.1 Review question

The review question was formulated according to the Population, Intervention, Comparator, Outcome (PICO) framework (presented in Table 1). The review seeks to answer the following question:

- What are the outcomes of newborn screening for SMA?

Two types of studies will be considered for this review:

- non-comparative studies, which report outcomes for population-based newborn bloodspot screening and contribute descriptive information on outcomes such as test performance.
- comparative studies of population-based newborn bloodspot screening for SMA versus no population-based screening, which compare clinical outcomes based on the intervention of screening.

These two types of studies will be considered separately in the review, as outlined below.

Table 1. Review question for assessing clinical effectiveness of NBS for SMA

Population	Newborns
Intervention	Population-based newborn bloodspot screening for SMA (including pilots).
Comparator	Non-comparative studies: ▪ no comparator (outcomes of screening cohort only described) Comparative studies: ▪ no population-based newborn bloodspot screening for SMA (patients with SMA presenting clinically).
Outcomes	Non-comparative studies: ▪ test performance ▪ case characteristics (for example, *SMN2* copy number, symptom status) ▪ pathway timings ▪ harms Comparative studies: ▪ clinical outcomes (for example, mortality and morbidity) ▪ pathway timings (for example, time to diagnosis, time to treatment) ▪ harms.
Study design	Include: ▪ case-control, cohort studies, and cross-sectional studies. Exclude: ▪ analytical performance studies and studies that do not report cases of SMA; non-human studies; papers not available in English or for which an adequate English translation cannot be obtained; letters, editorials, commentaries, preprints, and conference abstracts.

5.1.1 Eligible study design

Cross-sectional, case-control, cohort and case series studies will be eligible for inclusion.

5.1.2 Search methods

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

5.1.3 Data collection and analysis

Selection of studies

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

Both comparative studies (meaning studies comparing outcomes for patients with SMA identified by NBS to those identified in the absence of NBS), and non-comparative studies (meaning outcomes of a screening cohort only are described) will be included.

Data extraction and management

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

For the non-comparative studies, relevant data will include:

- population characteristics (country, sample size)
- test performance (for example, positive predictive values)
- number presymptomatic
- pathway timings (for example, time to diagnosis, time to treatment)
- harms
- incidence of SMA
- acceptability measures (for example, uptake rate)
- cascade identification (for example, identification of siblings with SMA).

For the comparative studies, relevant data will include:

- population characteristics (country, sample size)
- comparator
- mortality
- morbidity (for example, gross motor function)
- number presymptomatic
- pathway timings (for example, age at diagnosis, age at treatment, time to diagnosis, time to treatment)
- harms (for example, psychological impact on the family)
- screening acceptability measures (for example, uptake rate)
- cascade identification (for example, systematic offering of cascade testing to siblings of index cases).

Clinical outcomes will not be included for the 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.

Quality assessment

Each study will be assessed by one reviewer, with the assessment cross-checked by a second reviewer. The quality of each study will be assessed with tools appropriate to the respective study designs. Results will be summarised narratively.

Data synthesis

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

6 Cost effectiveness and affordability

6.1 Systematic review of cost-effectiveness studies

A systematic review of the literature on the cost effectiveness of newborn screening for SMA will be conducted. The findings of this review may adequately inform the question regarding the cost effectiveness of screening for SMA or may indicate the need for a de novo economic model (see section 6.2 below for associated criteria).

The associated Population, Intervention, Comparator, Outcomes, and Study design (PICOS) framework is provided in Table 2.

Table 2. PICOS framework for systematic review of cost-effectiveness studies

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

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

6.1.1 Search methods for identification of studies

Electronic searches will be conducted in Medline, Embase and the Cochrane Library. Electronic database searches will be supplemented by a search of grey literature including Google Scholar, national and HTA electronic sources. Reference lists of included studies will be searched for potentially relevant citations.

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

Study designs

Economic evaluations can be considered partial (that is, costing studies in which only the cost of healthcare interventions are analysed) or full (that is, studies in which both costs and consequences of two or more alternative strategies are compared).[25, 26] During scoping work completed to inform this protocol, it was noted that the majority of the economic analyses returned were in the form of cost-effectiveness analyses, cost-utility analyses (CUAs) and costing studies. In the interests of being able to assess the added value of the intervention relative to the

additional cost, only full economic evaluations will be considered (that is, cost-utility analyses or cost-effectiveness analyses). Where other forms of cost analyses are identified, these will not be retained for inclusion in the review of cost-effectiveness studies but will be retained for later consideration in informing the budget impact analysis.

Exclusion criteria

The following exclusion criteria will be applied:

- cost analyses and comparative resource use studies
- commentaries, letters, conference papers and abstracts where a detailed description of the methods is not available
- economic evaluations investigating the cost effectiveness of pharmacological treatments for SMA
- economic evaluations of prenatal or carrier screening for SMA
- analyses that simultaneously investigate the cost effectiveness of introducing multiple screening programmes (including screening for SMA), relative to no screening, unless disaggregated incremental costs and quality-adjusted life years (QALYs) are presented.

6.1.2 Data collection and analysis

Selection of studies

Titles and abstracts will be screened independently by two reviewers. The full text of potentially eligible studies will be retrieved and independently assessed for eligibility by two reviewers according to the criteria outlined in Table 2, with any disagreements being resolved by discussion or a third reviewer, if required.

Data extraction and management

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

The preferred outcome will be the cost per QALY gained. Other outcomes (for example, cost per life-year gained (LYG), cost per hospitalisation avoided, cost per death avoided) will also be extracted, where reported.

Assessment of methodological quality and transferability

Assessment of the methodological quality of economic evaluations will be carried out using the Consensus on Health Economics Criteria (CHEC)-list.[27] The ISPOR questionnaire will be used to assess the transferability potential of economic evaluations to the Irish setting.[28] This will be performed by two people

independently, with any disagreement resolved through discussion or a third reviewer, where necessary.

Data synthesis

Given the likely heterogeneity of studies in terms of population and healthcare system characteristics, and in line with previous assessments on this topic conducted internationally,[3, 17] results will be synthesised narratively. To facilitate comparability of the results across countries and years, costs will be inflated, where appropriate, and converted to Irish Euro in accordance with national HTA guidelines.[24]

Willingness-to-pay thresholds of €20,000 and €45,000 per QALY gained are typically used in Ireland as reference points for decision-making regarding reimbursement. Therefore, results will be presented in the context of both thresholds to facilitate comparisons across studies in terms of the interpretation of the results from the CUAs for the Irish context.

6.2 De novo economic evaluation

Contingent on the findings of the systematic review of cost-effectiveness studies described above, a de novo economic evaluation may be considered appropriate. This will be judged based on elements such as the applicability of international evidence to the Irish context, the availability of Irish data that may strengthen existing estimates, the potential for updates to the evidence base that may influence estimates of cost effectiveness and the overall added value of performing such analysis in terms of informing decision-making. If a de novo economic evaluation is considered necessary, this will be conducted to estimate the cost per quality-adjusted life year (QALY) gained of newborn screening for SMA, compared with usual care, in accordance with national HTA guidelines and Consolidated Health Economic Evaluation Reporting Standards (CHEERS) reporting guidelines.[9, 29]

6.3 Budget impact analysis and organisational implications

A budget impact analysis (BIA) will be undertaken to determine the additional investment required to include screening for SMA in the NNBSP. In line with national HTA guidelines,[30] the analysis will be carried out from the perspective of the publicly funded health and social care system in Ireland (that is, the HSE). Only direct costs to the HSE will be considered. Indirect costs such as productivity losses and out-of-pocket expenses incurred by families attending healthcare services will not be considered. However, wider societal impacts will be considered in the ethical analysis (section 7).

The analysis will estimate the incremental costs to the HSE associated with implementing this form of screening over a five-year time horizon. The comparator will be the current standard of care in Ireland.

Parameter data will be obtained from Irish data sources and published literature, as appropriate. Input from the HIQA EAG will be required to inform plausible values. In addition to the cost of tests and laboratory equipment, changes to organisational processes (for example, clinical pathways) resulting from the addition of SMA to the NNBSP will be identified and considered as part of the BIA. The additional resources required to implement SMA screening will be dependent on the available and planned resources at the time of implementation. Input from the EAG will be required to inform estimated resource requirements. Furthermore, potential cost offsets, such as prevention of hospitalisation, will also be considered and included, if sufficient data are available.

Where plausible estimates of uncertainty are available, sensitivity analyses will be conducted to assess the impact of uncertainty on the incremental budget impact.

Key parameter data required for the analysis may include:

- estimates of the target population and likely uptake rates
- estimates of the number of cases of SMA and instances of false positives likely to be identified by this form of screening programme
- capital investment for laboratory equipment (alongside necessary maintenance), laboratory space and storage, and any additional requirements to accommodate testing
- implementation costs (for example, consumables, verification, development of screening algorithms and pathways, information and communications technology (ICT) upgrades)
- potential requirements for recruitment and training of laboratory staff
- training and education for clinical staff involved in the delivery of the NNBSP
- costs for confirmatory testing and clinical evaluation
- treatment costs
- costs for updating NNBSP material and an information campaign
- any potential broader organisational issues associated with the sequential addition of conditions to the NNBSP, and the recent decision to implement screening for SCID.

The assessment of necessary organisational changes will be carried out in accordance with the EUnetHTA Core Model.[9] A description of the current pathway for the NNBSP, any anticipated changes in the organisation of care as a result of the introduction of screening for SMA, and the impact on existing activities will be provided. The impact of screening for SMA on various types of resources (such as,

equipment and supplies, facilities and human resources) will be considered as outlined above.

7 Ethical and social considerations

The ethical analysis will consider key social and moral norms and values relevant to newborn screening for SMA. Key ethical issues outlined in the EUnetHTA Core Model will be used to guide the ethical analysis.[9] Potential ethical issues may include issues related to:

- informed consent
- potential benefits associated with earlier diagnosis for those with SMA and hence earlier access to treatment
- the potential for missed cases
- potential for over-diagnosis and over-treatment in the case of SMA types with onset typically seen in adolescence and adulthood
- instances of false positives, the associated burden of confirmatory testing, and the related potential for emotional distress and anxiety
- communication of screening and confirmatory testing results
- any broader implications of screening for the family of the newborn.

References

1. CHI at Temple Street. A Practical Guide to Newborn Bloodspot Screening In Ireland: 9th edition 2022 [Available from: https://www.hse.ie/eng/health/child/newbornscreening/newbornbloodspotscreening/information-for-professionals/a-practical-guide-to-newborn-bloodspot-screening-in-ireland.pdf.
2. Health Service Executive. What you need to know about heel prick testing 2020 [Available from: https://www2.hse.ie/file-library/heel-prick-screening/what-you-need-to-know-about-heel-prick-screening.pdf.
3. Institut national d'excellence en santé et en services sociaux. Assessment of the relevance of neonatal screening for spinal muscular atrophy 2021 [Available from: https://www.inesss.qc.ca/fileadmin/doc/INESSS/Rapports/Depistage/INESSS_Amyotrophie_spinale_Avis.pdf.
4. 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.
5. 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.
6. Keinath MC, Prior DE, Prior TW. Spinal Muscular Atrophy: Mutations, Testing, and Clinical Relevance. Appl Clin Genet. 2021;14:11-25.
7. Jedrzejowska M. Advances in Newborn Screening and Presymptomatic Diagnosis of Spinal Muscular Atrophy. Degener Neurol Neuromuscul Dis. 2020;10:39-47.
8. 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.
9. European Network for Health Technology Assessment (EUnetHTA). HTA Core Model [Available from: https://www.eunethta.eu/hta-core-model/.
10. Department of Health. National Screening Advisory Committee: Recommendations 2021 [Available from: https://www.gov.ie/en/publication/5af1dd-national-screening-advisory-committee-recommendations/.
11. Health Information and Quality Authority. Review of processes in use to inform the expansion of newborn bloodspot screening programmes. 2021.
12. Loeber JG, Platis D, Zetterström RH, Almashanu S, Boemer F, Bonham JR, et al. Neonatal Screening in Europe Revisited: An ISNS Perspective on the Current State and Developments Since 2010. International Journal of Neonatal Screening. 2021;7(1).
13. Jansen ME, Metternick-Jones SC, Lister KJ. International differences in the evaluation of conditions for newborn bloodspot screening: a review of scientific literature and policy documents. European journal of human genetics : EJHG. 2016;25(1):10-6.
14. European Medicines Agency. Spinraza [2023]. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/spinraza.

15. European Medicines Agency. Evrysdi [Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/evrysdi.
16. European Medicines Agency. Zolgensma [Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/zolgensma.
17. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Newborn screening for 5q-linked spinal muscular atrophy. 2020.
18. Medical. C. Screening for spinal muscular atrophy External review against programme appraisal criteria for the UK National Screening Committee (UK NSC). 2018.
19. The Evidence-based Review Group. Evidence-based Review of Newborn Screening for Spinal Muscular Atrophy (SMA): Final Report 2018.
20. Cohen JF, Korevaar DA, Altman DG, Bruns DE, Gatsonis CA, Hooft L, et al. STARD 2015 guidelines for reporting diagnostic accuracy studies: explanation and elaboration. BMJ Open. 2016;6(11):e012799.
21. Campbell JM, Klugar M, Ding S, Carmody DP, Hakonsen SJ, Jadotte YT, et al. Diagnostic test accuracy: methods for systematic review and meta-analysis. JBI Evidence Implementation. 2015;13(3).
22. Whiting PF, Rutjes AW, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Annals of internal medicine. 2011;155(8):529-36.
23. 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.
24. Health Information and Quality Authority. Guidelines for Interpretation of Economic Evaluations 2014 [Available from: https://www.hiqa.ie/reports-and-publications/health-technology-assessments/guidelines-interpretation-economic.
25. 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.
26. van Mastrigt GA, Hiligsmann M, Arts JJ, Broos PH, Kleijnen J, Evers SM, et al. How to prepare a systematic review of economic evaluations for informing evidence-based healthcare decisions: a five-step approach (part 1/3). Expert review of pharmacoeconomics & outcomes research. 2016;16(6):689-704.
27. 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.
28. 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.
29. Husereau D, Drummond M, Petrou S, Carswell C, Moher D, Greenberg D, et al. Consolidated health economic evaluation reporting standards (CHEERS) statement. International journal of technology assessment in health care. 2013;29(2):117-22.

30. Health Information and Quality Authority. Guidelines for Budget Impact Analysis 2014 [Available from: https://www.hiqa.ie/reports-and-publications/health-technology-assessment/guidelines-budget-impact-analysis.
31. Department of Health. National Screening Advisory Committee: NSAC criteria 2020 [Available from: https://www.gov.ie/en/publication/c0d9f8-about-the-national-screening-advisory-committee/#nsac-criteria.

Appendix 1 NSAC criteria by HTA domain

Criterion No.	NSAC Grouping	Criterion	HTA domain(s)*
1	The Condition	The condition should be an important health problem. The epidemiology, incidence, prevalence and natural history of the condition should be understood, including development from latent to declared disease and/or there should be robust evidence about the association between the risk or disease marker and serious or treatable disease.	Epidemiology
2		All the cost-effective primary prevention interventions should have been implemented as far as practicable.	Not applicable**
3		If the carriers of a mutation are identified as a result of screening, the natural history of people with this status should be understood. The psychological implications should be considered, and the necessary psychological supports should be in place.	Epidemiology, Ethical, social and legal issues
4	The Screening Method	The screening method should be, as far as is practicable: a) simple b) safe c) precise d) reliable e) validated.	Clinical effectiveness and safety, Organisational issues
5		The distribution of screening values in the target population should be assessed and suitable cut-off levels/measurements defined and agreed by the applicant.	Description of technology, Clinical effectiveness and safety, Organisational issues
6		The screening process should be acceptable to the target population.	Ethical, social and legal issues
7		There should be an agreed policy on the further diagnostic investigation of individuals with a positive screening result and on the choices available to those individuals.	Description of technology, Organisational issues

Criterion No.	NSAC Grouping	Criterion	HTA domain(s)*
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.

Source of NSAC criteria: Department of Health[31]

* 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).[9] The mapping exercise aimed to clarify the extent to which a typical HTA addresses the NSAC criteria, and which HTA domain addresses which criterion/criteria.

** Considered outside the scope of a conventional HTA, unless the HTA is undertaken specifically to inform this criterion.

Appendix 2: Provisional search strategy

Combined provisional search strategy for clinical effectiveness and cost-effectiveness of screening for SMA

Medline (EBSCO, 1 January 2023)		
#	**Query**	**Results**
S16	S14 AND S15	266
S15	S1 OR S2 OR S3 OR S4	8,981
S14	S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13	51,514
S13	TI Guthrie OR AB Guthrie	867
S12	AB DBS OR TI DBS	12,736
S11	AB heel-stick OR TI heel-stick	249
S10	AB (heel prick OR heel-prick) OR TI (heel prick OR heel-prick)	389
S9	AB ("dried blood spot" OR "dry blood spot") OR TI (dried blood spot" OR "dry blood spot)	2,233
S8	AB (newborn or "newly born" or neonat* or infant) N3 (test* OR screen*)) OR TI ((newborn or "newly born" or neonat* or infant) N3 (test* OR screen*))	28,666
S7	(MH "Dried Blood Spot Testing")	2,011
S6	(MH("Mass Screening+") AND (MH "Infant, Newborn+")	17,405
S5	(MH "Neonatal Screening")	11,663
S4	AB (Werdnig-Hoffmann OR "Werdnig Hoffmann" OR Kugelberg-Welander OR "Kugelberg Welander" OR "progressive muscular atrophy of infancy") OR TI (Werdnig-Hoffmann OR "Werdnig Hoffmann" OR Kugelberg-Welander OR "Kugelberg Welander" OR "progressive muscular atrophy of infancy")	439
S3	TI "spinal muscle atroph*" OR AB "spinal muscle atroph*"	89
S2	AB spinal N3 muscular atroph* OR TI spinal N3 muscular atroph*	6,962
S1	(MH "Muscular Atrophy, Spinal+")	6,217
Embase (Elsevier, 30 January 2023)		
#	**Searches**	**Results**
#17	#5 AND #14 NOT ([conference abstract]/lim OR [conference paper]/lim OR [conference review]/lim)	364
#16	#5 AND #14 AND ([conference abstract]/lim OR [conference paper]/lim OR [conference review]/lim)	170
#15	#5 AND #14	534
#14	#6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13	48,612

# 13	guthrie:ab,ti	1,162
# 12	'heel-stick':ab,ti	309
# 11	'heel prick' OR 'heel prick':ab,ti	521
# 10	'dried blood spot' OR 'dry blood spot':ab,ti	7,760
# 9	((newborn OR 'newly born' OR neonat* OR infant) NEAR/3 (test* OR screen*)):ab,ti	28,589
# 8	'dried blood spot testing'/exp	5,668
# 7	'mass screening'/exp AND 'newborn'/exp	18,526
#6	'newborn screening'/exp	22,071
#5	#1 OR #2 OR #3 OR #4	68,628
#4	'werdnig hoffmann' OR 'kugelberg welander' OR 'progressive muscular atrophy of infancy':ab,ti	2,075
#3	'spinal muscle atroph*':ab,ti	149
#2	(spinal NEAR/4 'muscular atroph*'):ab,ti	10,132
#1	'spinal muscular atrophy'/exp	67,340

Cochrane Library (30 January 2023)

#	Search	Results
#1	MeSH descriptor: [Muscular Atrophy, Spinal] explode all trees	110
#2	(spinal NEAR/3 muscular atroph*):ti,ab,kw (Word variations have been searched)	342
#3	("spinal muscle atroph*"):ti,ab,kw (Word variations have been searched)	0
#4	(Werdnig-Hoffmann OR 'Werdnig Hoffmann' OR Kugelberg-Welander OR 'Kugelberg Welander' OR 'progressive muscular atrophy of infancy'):ti,ab,kw (Word variations have been searched)	52
#5	#1 OR #2 OR #3 OR #4	348
#6	MeSH descriptor: [Neonatal Screening] explode all trees	140
#7	MeSH descriptor: [Mass Screening] explode all trees	4212
#8	MeSH descriptor: [Infant, Newborn] explode all trees	17921
#9	#7 AND #8	213
#10	MeSH descriptor: [Dried Blood Spot Testing] explode all trees	31
# 11	((newborn or 'newly born' or neonat* or infant) NEAR/3 (test* OR screen*)):ti,ab,kw (Word variations have been searched)	2189
#12	(('dried blood spot' OR 'dry blood spot')):ti,ab,kw (Word variations have been searched)	528
#13	(heel prick OR heel-prick OR heel-stick):ti,ab,kw (Word variations have been searched)	304
#14	(DBS):ab (Word variations have been searched)	1424
#15	("Guthrie"):ti,ab,kw (Word variations have been searched)	43

#16	#6 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15	4247
#17	#5 AND #16	13

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