UK National Screening Committee

DRAFT

Specification document: Scoping work for a decision analytic model and cost effectiveness evaluation of newborn screening for SMA

Background

Spinal Muscular Atrophy (SMA) is an autosomal recessive neurodegenerative disease that affects the control of muscle movement, primarily affecting ability to crawl and walk, move the arms, hands, head, neck, and to breathe and swallow. It is characterised by degeneration of specialised nerve cells, called motor neurons, leading to a progressive atrophy of skeletal muscle. SMA represents the second most common fatal autosomal recessive disorder after cystic fibrosis. An estimated 1,200 people in the UK have a form of SMA with a carrier frequency of 1 in 40-60.[1,2,3] SMA can be caused by mutations in the SMN1, UBA1,[*] DYNC1H1,[†] and VAPB[‡] genes. The most common of such mutations (95% of cases) is the absence of SMN1 gene exon 7, located on chromosome 5q13in, which is responsible for the production of proteins that are essential to motor neurons. A second centromeric SMN gene (SMN2 or SMNc) is also present in the chromosome, can partially compensate for the loss of SMN protein cause by mutations in the SMN1 and is considered in the diagnostic criteria of SMA.

SMA is classified traditionally into five types according to age of onset and the severity of the condition is based on motor function test (SMA types 0, 1, 2, 3, and 4). This clinical subtype classification was established before the genetic origin of SMA was understood. Mutations in the SMN1 gene have now been associated with all subtypes of SMA with no clear phenotype – genotype correlation. It is also recognised that the phenotype of SMN1-associated SMA is a continuum with no clear demarcations between subtypes. It is worth noting that the international standards of care for SMA refer to the impact of SMA on motor function as a guide to care and management needs, rather than the traditional classification based on the age at disease onset or the highest historically achieved motor function[4]. This proposed work focuses only on 5q SMA. There are some sub-types of SMN-related SMA but they have entirely different aetiology and presentation, and they will not be considered in this work.

[*] The **UBA1 gene** (also called UBE1) provides instructions for making the ubiquitin-activating enzyme (E1). This enzyme is involved in a process that targets proteins to be degraded within cells. The reduced or absent levels of functional E1 results in the build-up of proteins in the cell can cause it to die. Motor neurons are particularly susceptible to damage from protein build-up which causes their degeneration.

[†] The **DYNC1H1 gene** provides instructions for making a protein that is part of a group (complex) of proteins called dynein. Dynein are cytoskeletal motor proteins present in the cell cytoplasm where they are part of a network that moves proteins and other material. In neurons, dynein moves cellular materials away from the synapses to the centre of the cell, helping the communication between neurons. DYNC1H1 gene mutations disrupt the function of the dynein complex which results with a decrease in chemical messaging between neurons that control muscle movement leading to muscle weakness and wastage.

[‡] The **VAPB gene** provides instructions for making a protein that is found in cells throughout the body. It is unclear how a VAPB gene mutation leads to the loss of motor neurons; however, adult-onset form of is associated with such mutation.

The combination between the deletion of the SMN1 gene and the number of extra copies of the SMN2 gene is associated with the severity of SMA. For example, some people with type 2, 3, or 4 spinal muscular atrophy (less severe forms of the disease) have three or more copies of the SMN2 gene in each cell.

SMA type 0: It is the most severe form of SMA. It affects newborns, with the onset of disease occurring in utero. Babies affected by SMA Type 0 have a life expectancy that usually does not extend beyond the neonatal period.[5] Symptoms can often be seen in the later stages of pregnancy, including reduced foetal activity.

SMA type 1 (Werdnig–Hoffman disease): Is the most common subtype of the disease accounting for up to 50% of all cases of SMA. [6,7] The most common genotype for this type is homozygous SMN1 deletion in the presence of two functional copies of the SMN2 gene. Signs of the disease usually become apparent within 4 to 5 months of life. Babies affected by SMA Type 1 are developmentally delayed; most are unable to support their head or sit unassisted, hence it is often referred to as 'floppy baby syndrome'. Children with this type have breathing and swallowing problems that can lead to choking/gagging and which typically results in eventual reliance on respiratory support and tube feeding. Life expectancy is usually less than two years.

SMA type 2 (Dubowitz disease): This intermediate form of the disease is characterised by muscle weakness that typically develops in children between 6 and 18 months of age. There are some children with type 2 SMA that learn to stand (even though they cannot walk) at the expected age, but quickly lose the ability as their bodies become heavier and the demand on muscle increases. Their life expectancy is typically understood to be shorter than that of the healthy population (reported between 2 to 40 years). However, due to therapeutic progress and improvements in medical care, the quality and life expectancy of adults with type II SMA have improved.[8] Many individuals can expect to have near-normal life spans, particularly those at the type III end of the type II spectrum.[9]

SMA type 3 (Kugelberg–Welander disease): The onset of this disease usually occurs sometime between 12 months of age and adulthood. Such individuals are able to stand and walk unaided, but walking and climbing stairs may become increasingly difficult with age. Respiratory involvement is less noticeable, and life expectancy is normal or near normal. However, it is worth distinguishing between type 3a (18 months to three years of age) and type 3b (three to 18 years of age)[§]. Some children with the clinical diagnosis type 3a are impacted at a younger age as severely as those who are clinically diagnosed as type 2. The majority lose their ability to walk in their teens.

SMA type 4: this is a late-onset disease that manifests usually in adulthood, often after 30 years of life. Individuals with SMA type 4 usually have mild to moderate muscle weakness, tremor, twitching, or mild breathing problems that can lead to mobility problems requiring the

[§] Spinal Muscular Atrophy UK. Symptoms, Diagnosis & Effects of 5q Spinal Muscular Atrophy. Available at: https://smauk.org.uk/symptoms-diagnosis-effects-of-5q-sma (Accessed 10 March 2022)

individual to eventually use a wheelchair. Other complications associated with the condition are rare, and the life expectancy is comparable to that of healthy individuals.

SMA is a recessive condition, therefore, individuals are called 'carriers' when they have one healthy copy of SMN 1 gene and one faulty, but do not present any symptoms. They can pass on to their children the faulty gene, so that, when two 'carriers' have a child together there is a 1 in 4 chance (25%) that their child will have SMA; 1 in 4 chance (25%) that their child will be healthy; and 1 in 2 chance (50%) that the child will be also a 'carrier'.

In the context of SMA there are three common carrier mutation categories (see table 1).

Table 1. SMA carrier mutation categories

Mutation category	SMN1 exon 7 copy number	Genotype designation
Category 1	Only 1 copy of SMN1	[1 + 0] or 2ab
Category 2	Two copies of SMN1 on one chromosome 5 and a deletion/conversion mutation of SMN1 on the other chromosome 5	[2 + 0] or 2ac
Category 3*	2 or	[1 + 1[d]] or 2bd
	≥2 Intragenic mutation on one chromosome resulting in an SMN1 exon 7 copy number of _2	[1 + 1[d]] or 2cd

* SMN1 exon 7 copy number in Category 3 may depend on the location of the point mutation within the SMN1 gene and its ability to interfere with copy number analysis

Current recommendation

The UK NSC recommendation is that a universal screening for SMA should not be introduced.

The most recent UK NSC review process was completed in 2018. This addressed prenatal genetic carrier screening, antenatal screening and newborn screening. In relation to newborn screening the review reported that:

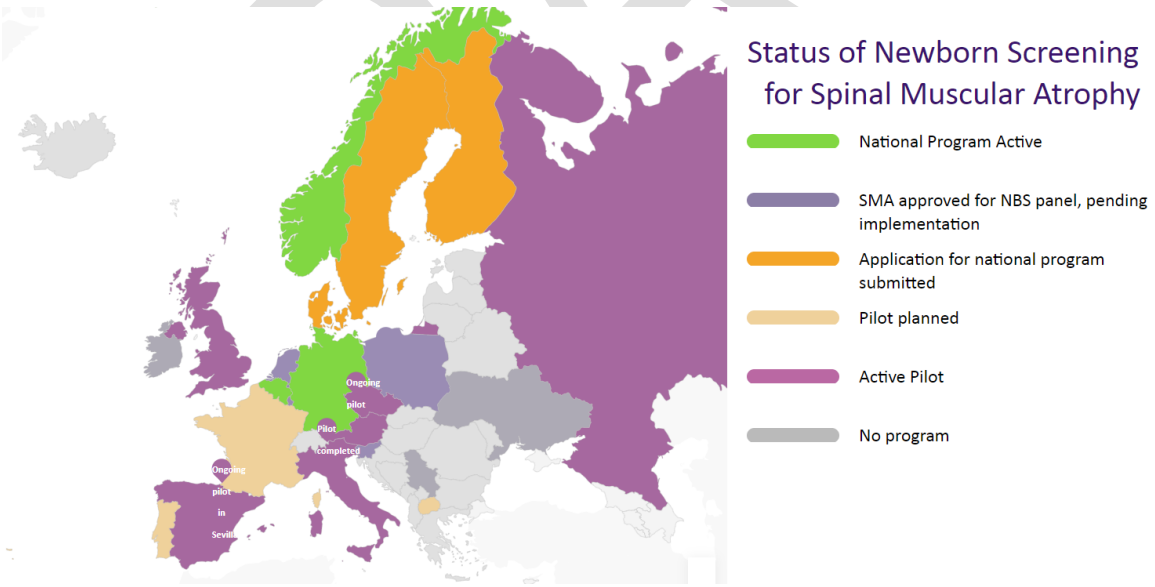
- There was still insufficient information about the incidence and prevalence of SMA, or how many people are affected by each type of SMA (and in consequence what level of severity) in the UK.

- Four studies reported on SMA newborn screening tests. Two studies found that mCOP-PCR and HRM analysis are highly sensitive and specific newborn SMA screening methods. However, overall the evidence base had a high or unclear risk of bias and it was mainly based on small population screening studies, in populations that might not reflect the general population.
- Only one treatment, nusinersen (which is marketed as Spinraza™), was found showing promising results suggesting that nusinersen is effective in improving outcomes for patients with SMA. Two high-quality RCTs reported better outcomes on measures of motor control in patients with infantile-onset and later-onset SMA given nusinersen compared to sham control. However, the evidence base was limited with studies still ongoing, and therefore, there was a lack of data for the long-term effectiveness and safety of the treatment.
- There was no high-quality evidence for an optimal management pathway for SMA patients identified through screening, so the benefits of pre-symptomatic treatment compared to treatment following symptom onset were unclear.

Current landscape of SMA screening

Below is a Figure showing the current status of SMA screening status across Europe.

Figure 1. Current status of SMA screening status across Europe



Source: SMA NSB Alliance (https://www.sma-screening-alliance.org/map/)

UK NSC stakeholder discussion and workshop on screening for SMA

Since the 2018 UK NSC evidence summary, the SMA screening landscape has changed significantly. Discussion with stakeholders identified developments affecting the concept of, and case for, newborn screening for SMA.

For example, nusinersen and, since the last review, another drug (onasemnogene abeparvovec (Zolgensma™)) has been made available in the NHS. In Scotland, both drugs have been approved for use. In England, the National Institute for Health and Care Excellence (NICE) has recommended that the effectiveness of both drugs should be further evaluated before a final recommendation is made. This is being taken forward within Managed Access Agreements (MAA)** which makes them available for use in presymptomatic SMA. Other drugs are in development. Because of this, the debate about newborn screening is no longer about whether to screen despite the absence of disease modifying interventions. It is about whether screening does more good than harm at reasonable cost compared to clinical detection.

In addition, a small UK case control (two gate) study of the accuracy of PCR based screening has been undertaken and published. This is being followed up with a large cohort study of the accuracy and feasibility of PCR based screening in the UK. Because of this, the quality of test accuracy data from the UK will be improved in comparison with most other UK NSC reviews.

These, and other, developments were discussed at a UK NSC stakeholder workshop in July 2021. It was noted that the UK NSC needs to review the evidence relating to newborn screening for SMA as part of its triennial review cycle. The recent developments suggest that evidence maps, or evidence summaries alone may not be appropriate products for the forthcoming review and that a more comprehensive statement on the effectiveness of screening for SMA is needed. In the absence of direct trial evidence, the UK NSC is increasingly using decision analytic models for this purpose in its work on rare diseases. However, the evolving situation in relation to the test and treatments for SMA means that the ability to develop and populate a model to generate reliable outputs is uncertain.

Aim and objectives of this work

The purpose of this work is to prepare for a modelling study by:

- Objective 1: Conducting a review of available decision analytic modelling studies and cost effectiveness evaluations which address newborn screening for SMA in the era of novel treatments
- Objective 2: Developing an evidence map of published studies and evaluations of PCR based screening and treatment in presymptomatic SMA
- Objective 3: Proposing a plan for a modelling study with clinical and cost effectiveness outcomes

** Overview | Nusinersen for treating spinal muscular atrophy | Guidance | NICE

Overview | Onasemnogene abeparvovec for treating spinal muscular atrophy | Guidance | NICE

This range of products will enable the UK NSC to understand the current developments with reference to the evidence base in key areas, gain an insight into existing work to explore the clinical and cost effectiveness of screening, to prepare to commission a modelling and cost effectiveness exercise when appropriate and to maintain the dialogue with stakeholders.

Specific information

The work will be undertaken in liaison with the UK NSC Evidence Team and will report to UK NSC Fetal, Maternal and Child Health (FMCH) Reference Group at appropriate intervals. The work should be taken forward transparently using expert workshops as required. Attendees at the recent UK NSC SMA workshop would be an obvious source of expertise. Some further information for each of the objectives is provided below. In your proposal, please state how you would approach the objectives and how you would involve stakeholders.

Objective 1. Review of modelling studies

Modelling studies are available.[††] However, to our knowledge, no UK modelling study has been undertaken to estimate the clinical and cost effectiveness of newborn screening for SMA. The purpose of this initial review of existing modelling studies is to help the UK NSC develop a model and, in particular, to stimulate discussion with stakeholders on key issues which will inform a modelling and cost effectiveness project in the future.

The resulting document should be based on the UK NSC template for evidence summaries (see appendix 1). The final protocol of the review should be agreed with the UK NSC Evidence Team but should report:

- decision problem – population, interventions, comparators, outcomes (clinical and cost effectiveness), settings
- methods – model type, perspective, time horizon, discount rates, resource use and costs considered, measurement of valuation of preference based outcomes, assessment / characterisation of uncertainty (eg parameter, heterogeneity, methodological, structural), data sources for key parameters (for example natural history, test performance, treatment effectiveness, qualitative outcomes), assumptions made.
- results and limitations

[††] Shih STF, Farrar MA, Wiley V, et al. J Neurol Neurosurg Psychiatry doi:10.1136/jnnp-2021-326344,
Jalali A et al, Cost-Effectiveness of Nusinersen and Universal Newborn Screening for Spinal Muscular Atrophy, J Pediatr 2020;227:274-80

Objective 2: Evidence map of published studies and evaluations of PCR based screening and treatment in presymptomatic SMA

The purpose of an evidence map of published studies and evaluations of PCR based screening and treatment in presymptomatic SMA is to provide a basic overview of the volume and type of evidence on these two key issues which has become available since the previous, 2018, UK NSC review. This will inform discussion on the, mainly, non-UK evidence which might be used as source material in a modelling study.

The resulting document should be based on the UK NSC template for evidence maps. A separate brief for this objective is attached at appendix 2.

Objective 3. Proposing a plan for a modelling study

The purpose of this part of the work is to develop the core materials needed to commission a modelling study. It is anticipated that this will build on objectives 1 and 2 and that stakeholder / expert workshops and meetings will form a key part of this part of the work. There are two main components:

i. Model Specification

This should refer to the review of existing models as objective 1.

The model specification should include the model scope, type and structure, required data, outcomes, analytical approach and other methodological information, as necessary. This specification should be developed with reference to key items on the CHEERS checklist[‡‡] and agreed in discussion with the UK NSC Evidence Team.

The interventions/comparators for the model need to be discussed and finalised with the UK NSC Evidence Team and experts in the field. For example, the model may need to compare newborn screening followed by the use of:

- individual drugs versus best supportive care in an unscreened population
- individual drugs versus use of the same drug in an unscreened population
- one drug versus a different drug

It is anticipated that this, and other aspects of the specification, will require significant interaction with experts in the field. In addition, NICE have recently completed significant projects on two of the novel drugs for SMA and this may be informative for the current project. The UK NSC Evidence Team would be available to help with identifying and approaching a group of experts to contribute to this project.

‡‡ Husereau D, Drummond M, Petrou S, Carswell C, Moher D, Greenberg D, et al. Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement. BMJ : British Medical Journal. 2013;346:f1049.

ii. Strategy for populating the model

This part of the work will provide an assessment of the data sources required to populate the model and their availability or development requirements. Sources may include primary research studies, existing or de novo evidence syntheses, national, regional and local datasets, evidence maps, NHS costing sources.

It is anticipated that data on health state / utility values will be particularly problematic and that comparative data on outcomes (short- and long-term) will be limited in volume. Strategies to deal with issues such as this in the model should be addressed in the resulting output.

Project outcome

The project outcome will be a report, with the outputs of objectives 1 & 2 as appendices, which can be used in a separate tendering process to commission a team to develop and populate a model and report the results to inform a recommendation on newborn screening for SMA. The successful team for this work will be eligible to bid for the next steps.

Project management

Regular online meetings between the Provider's project team and the UK NSC project team will be scheduled throughout the duration of the contract. The frequency of these meetings will be decided by the Authority in collaboration with the Provider.

Timelines

To be outlined in the final version of the specification document.

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Appendix 1: PICOs for Objective 1 (to be refined and confirmed with reviewers) – review of modelling studies

The output for objective 1 will be an evidence summary. This will be conducted using rapid reviews methodology in accordance to the UK NSC evidence review process https://www.gov.uk/government/publications/uk-nsc-evidence-review-process/uk-nsc-evidence-review-process . The UK NSC Reporting Checklist for Evidence Summaries (ReCESs) will be used to ensure transparency in the reporting methods for the evidence summary review process.
The appointed contractor must use the UK NSC document template(s) and follow the Authority 'document formatting guidelines' provided below.
The template(s) has been specifically formatted to fulfil the legal obligation to comply with the accessibility regulations. Therefore, all documents that are produced by the contractor to fulfil the requirements of this contract must be submitted to the Authority in the indicated template. Further information can be found on: https://accessibility.campaign.gov.uk
Where the documents fail to meet such a requirement the Authority will revert to the contractor such documents to resubmit them in accordance with the above guidelines.
Failure to meet these requirements would be considered a breach of contract.


Evidence summary final_Oct 2021.odt


UK NSC document formatting guidelines.

Question	**How have modelling studies and cost effectiveness analyses addressed newborn screening for SMA in the era of novel treatments?**
Notes	The review should report the way in which the decision problem has been defined, the methods employed and the results / limitations which have been reported.
Review methodology	Rapid review, in line with the requirements for Evidence Summaries
Population	Newborns
Intervention	Newborn screening for SMA
Comparator	No newborn screening Cascade screening
Outcomes	• Total cost of screening for SMA • Incremental cost • Incremental life-years gained • Gain in other clinical outcomes as defined by the study

	• Incremental cost-effectiveness ratio (ICER) • Number of lives saved • Cost per life saved • Any other outcome as outlined by the study
Study designs	Decision analytic models and economic evaluations i.e. studies comparing at least two alternative interventions in terms of costs and outcomes. Cost-minimization, cost-effectiveness, cost-utility, cost-benefit and cost-consequence analyses can all be considered. Reviews of economic evaluations can also be included.
Date and language of publication	English language published since January 2015 (to be discussed, this is to ensure that no studies which include novel treatments are missed)
Formal quality appraisal	Tool to be decided by reviewer
Example papers	Shih STF, Farrar MA, Wiley V, et al. J Neurol Neurosurg Psychiatry doi:10.1136/jnnp-2021-326344 Jalali A et al, Cost-Effectiveness of Nusinersen and Universal Newborn Screening for Spinal Muscular Atrophy, J Pediatr 2020;227:274-80 Chen et al. Value Health. 2020. Volume 23, Supplement 1, S2 Arjunji et al. Value in Health 2020. Volume 22, Supplement S75
UK NSC criteria	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 this criterion should have regard to evidence from cost benefit and/or cost effectiveness analyses and have regard to the effective use of available resource.

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Appendix 2: PICOs for Objective 2 (to be refined and confirmed with reviewers) – evidence map of published studies and evaluations of PCR based screening and treatment in presymptomatic SMA

The aim of this document is to prepare an evidence map to identify whether there is any new evidence to suggest that the volume of evidence on the test and treatment for SMA has increased since the last UK NSC review in 2018.

An evidence map is a rapid evidence product which aims to gauge the volume and type of evidence relating to a specific topic. A systematic literature search is undertaken and titles and abstracts are sifted to identify the relevant literature. For some references, the full-text may be reviewed for clarity. Evidence maps are usually used by the UK NSC to establish if there is sufficient evidence to justify a larger review with a more sustained analysis. In this case, it should be used as one input to the discussion on whether a modelling exercise is likely to be justified in the immediate term.

For more information on what an evidence map involves, see the evidence map template and an example of a UK NSC evidence map below:


UK NSC evidence map_Oct 2021_Final.d


Evidence_map_-_ALD_2021.pdf

The appointed contractor must use the UK NSC document template(s) and follow the Authority 'document formatting guidelines' provided in Appendix 1.
The template(s) has been specifically formatted to fulfil the legal obligation to comply with the accessibility regulations. Therefore, all documents that are produced by the contractor to fulfil the requirements of this contract must be submitted to the Authority in the indicated template. Further information can be found on: https://accessibility.campaign.gov.uk
Where the documents fail to meet such a requirement the Authority will revert to the contractor such documents to resubmit them in accordance with the above guidelines. Failure to meet these requirements would be considered a breach of contract.

Questions to be addressed in the evidence map

Question 1	What is the volume and type of evidence available on PCR based testing for newborn screening for Spinal Muscular Atrophy?
Note	This question should provide information on UK and international studies reporting: • Tests accuracy outcomes • Logistic / feasibility outcomes
Population	Neonatal

Index test	PCR based newborn screening using dried blood spots (DBS)
Comparator	Any alternative approach to newborn screening using DBS Any alternative PCR method e.g. two-tier vs single tier None
Reference standard	For screen positives – confirmatory genetic testing e.g. multiplex ligation-dependent probe amplification (MLPA) For screen negatives – clinical reporting / follow up or none Or any other specific "gold standard," as determined by the study itself
Target condition	5q Spinal Muscular Atrophy
Outcomes	• Sensitivity • Specificity • False positive rate • False negative rate • Positive predictive values (PPV) • Negative predictive values (NPV) • Likelihood ratios • Area under the curve • Clinical or logistic outcomes – e.g. time to diagnosis, time to treatment, laboratory or clinic workload, by product / incidental findings
Study design	Studies reporting clinical validity measures, and systematic reviews of these: Comparative and / or observational studies e.g. randomised controlled trials, cohort studies, case control (two gate) studies and systematic reviews (SRs) of these. A hierarchical approach should be taken: studies in randomly assigned or consecutively enrolled populations and systematic reviews of these should be prioritised. If none or few of these designs are found, other study designs should be reported, for example case-control studies. Prospective studies with nested cases should be included.
Language and date	English language published since January 2018
UK NSC criteria	4. There should be a simple, safe, precise and validated screening test

Question 2	What is the volume and type of evidence on the effectiveness of pharmacological treatment for Spinal Muscular Atrophy in presymptomatic SMA?
Sub-questions	Analysis of the papers is not necessary as this is an evidence map but papers addressing the following are of particular interest: • Is the pharmacological treatment for Spinal Muscular Atrophy equally effective for all Spinal Muscular Atrophy types? • Are pharmacological treatments for SMA more effective if administered in presymptomatic SMA?
Population	Individuals with SMA
Intervention	Pharmacological treatment administered presymptomatically
Comparator	Normal care Pharmacological treatment (same as Intervention above) administered following symptomatic presentation Pharmacological treatment (different to Intervention above) administered presymptomatically None
Outcomes	• Quality of life • Improved mobility (preventing joint stiffness, and improving flexibility and range of movement) • Improved breathing • Nutrition and feeding (avoiding problems such as dehydration and ensure healthy development) • Decrease in respiratory complications (fatal breathing problems caused by a weakening of the respiratory muscles and respiratory tract infections) • Increased life expectancy
Study design	RCTs prioritised, prospective comparative and non comparative observational studies. Also systematic reviews of these studies.
Language and date	English language published since January 2018
UK NSC criteria	9. There should be an effective intervention for patients identified through screening, with evidence that intervention at a pre-symptomatic phase leads to better outcomes for the screened individual compared with usual care. Evidence relating to wider benefits of screening, for example those relating to family members, should be taken into account where available. However, where there

	is no prospect of benefit for the individual screened then the screening programme should not be further considered. 10. There should be agreed evidence based policies covering which individuals should be offered interventions and the appropriate intervention to be offered.

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Appendix 3: Scope for Objective 3 (to be refined and confirmed with reviewers/modellers)

The aim of objective 3 is to propose a plan for a future modelling study. The model will need to estimate the clinical and cost effectiveness of newborn screening for SMA. This model scoping exercise can be used as a starting point for a future UK NSC modelling project but it also acts as a minimum requirement / reference for objective 1 (review of available cost effectiveness evaluations of SMA screening) and a measure of whether there is a model out there which could be re-used or whether a de novo model required.
This question is related to UK NSC population screening criterion 18:

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 this criterion should have regard to evidence from cost benefit and/or cost effectiveness analyses and have regard to the effective use of available resource.

Potential scope

This model will project and compare the health benefits, harms, resource use and costs associated with newborn screening for SMA. The scope of the decision problem is outlined below.

Target population and subgroups	Population: UK newborn population Subgroups: UK newborns with SMN1 deletion but different SMN2 copy numbers
Setting and location	UK Screening Programme – complex intervention spanning primary, secondary and tertiary care
Perspective on health outcomes	All direct health effects, to patients, family members, and informal carers
Perspective on costs	Cost to the UK National Health Service and Personal Social Services
Intervention	PCR based newborn screening followed by treatment with: • Onasemnogene abepavovec (Zolgensma) • Nusinersen (Spinraza) • Other available treatments
Comparator	Work to identify the most appropriate comparator will be required but the following should be considered: • best supportive care in an unscreened population • use of the same drug in an unscreened population • head to head with a different drug also in a screened population

Time horizon	Lifetime
Health outcomes: benefits and harms	Mortality Age appropriate motor function Health related quality of life Speech / communication Respiratory function / ventilation requirement (invasive / non-invasive) Skeletal / muscular complications Hospitalisation Diagnostic odyssey / journey False positives Variants of uncertain significance Overtreatment / mis-directed treatment Overdetection / detection of adult onset SMA Adverse effects of treatment
Clinical and cost-effectiveness outcomes	Incremental costs (exploded view for clear presentation of logistic burden of a screening programme) Incremental clinical effectiveness (as measured by benefits and harms in health outcomes section) Incremental cost-effectiveness ratios (cost per LY and QALY) Expected value of perfect information (EVPI) analysis
Discount rate	Health benefits – 3.5% Costs – 3.5%

As a reminder to the Provider, the purpose of this part of the work (objective 3) is to develop the core materials needed to commission a modelling study. Objective 3 should therefore be developed bearing in mind the model specifications outlined in the table above and the requirements listed below.

The model should be reported using the CHEERS checklist.

Some points for consideration are highlighted below:

Model structure

This should be justified with reference to the natural history and clinical pathway.

Clinical effectiveness sources

If possible, systematic review and meta-analysis should be used to estimate the clinical effectiveness of screening and treatment. Use of published systematic reviews undertaken elsewhere should be justified.

Parameters, and their sources, relating to clinical effectiveness which are not included in the systematic review should be presented. These might include studies which are less directly relevant to the clinical effectiveness of screening, but which can be linked for modelling purposes.

Costs and resource use

Costs and resource use (e.g. those associated with the intervention, comparators, health states and harms) should be presented along with their sources.

Logistic measures and associated costs should be presented clearly to enable an assessment of the feasibility of screening.

Clinical / expert opinion

Inputs and assumptions defined with reference to expert opinion should be clearly identifiable from those derived from published sources.

The mechanism for incorporating these into the model should be described (e.g. selection of experts, extrapolation of primary study outcomes beyond the study follow up period).

Utility values

The sources of utility values and their application in the model should be described.

Base case

The base case should be presented to enable comparison with the scope of the decision problem.

Sensitivity analyses

Decision uncertainty should be quantified through probabilistic sensitivity analysis (PSA).

Deterministic sensitivity analysis should be used to explore the model's sensitivity to variation in individual parameters or limited sets of parameters. Selection of parameters should be justified by the importance of the parameter/s in the model. Examples of potential sensitivity analyses:

- uptake of screening
- adherence of population to the diagnostic and treatment pathway
- proportion of SMA babies detected via family history

Scenario analyses should be used to explore uncertainty about structural assumptions.

[1] Cusin, V., Clermont, O., Gérard, B., Chantereau, D. and Elion, J. (2003) 'Prevalence of SMN1 deletion and duplication in carrier and normal populations: implication for genetic counselling', Journal of Medical Genetics, 40(4), e39.

[2] Sheng-Yuan, Z., Xiong, F., Chen, Y.J., Yan, T.Z., Zeng, J., Li, L., Zhang, Y.N., Chen, W.Q., Bao, X.H., Zhang, C. and Xu, X.M. (2010) 'Molecular characterization of SMN copy number derived from carrier screening and from core families with SMA in a Chinese population', European Journal of Human Genetics, 18(9), pp. 978-984.

[3] Hendrickson, B.C., Donohoe, C., Akmaev, V.R., Sugarman, E.A., Labrousse, P., Boguslavskiy, L., Flynn, K., Rohlfs, E.M., Walker, A., Allitto, B., Sears, C. and Scholl, T. (2009) 'Differences in SMN1 allele frequencies among ethnic groups within North America', Journal of Medical Genetics, 46(9), pp. 641-644.

[4] Mercuri E, et al. SMA Care Group. Diagnosis and management of spinal muscular atrophy: Part 1: Recommendations for diagnosis, rehabilitation, orthopedic and nutritional care. Neuromuscul Disord. 2018 Feb;28(2):103-115. doi: 10.1016/j.nmd.2017.11.005. Epub 2017 Nov 23. PMID: 29290580.

[5] Mercuri, E., Bertini, E. & Iannaccone, S. T. Childhood spinal muscular atrophy: controversies and challenges. Lancet Neurol. 11

[6] Faravelli et al. 2015. SMA-recent therapeutic answers for an old challenge; Nat Rev Neurol. 2015 Jun;11(6):351-9.

[7] MSA support UK http://www.smasupportuk.org.uk/sma-type-1-information

[8] Matthew et al. Assessing the Needs of the SMA Population: Survey Results of Health Care Providers and Families; SAGS Open; 2004.

[9] Roulault et al. Disease impact on general well-being and therapeutic expectations of European Type II and Type III spinal muscular atrophy patients; Neuromuscular Disorders, 2017 Volume 27, Issue 5, Pages 428–438