UK National Screening Committee

Screening for Spinal Muscular Atrophy (SMA)

31 October 2018

Aim

1. To ask the UK National Screening Committee (UK NSC) to make a recommendation, based on the evidence presented in this document, whether or not screening for Spinal Muscular Atrophy (SMA) meets the UK NSC criteria for a systematic population screening programme.

Current recommendation

2. The 2013 UK NSC review of screening for SMA concluded that systematic population screening is not recommended.

3. This was because the 2013 review concluded that:

    - Insufficient evidence was identified on the epidemiology of SMA, including the number of people affected by the disease overall and the specific disease types, the acceptability of screening and the psychosocial implications of screen-detected carrier status.

    - Although evidence was identified for dosage analysis as the main method by which to determine carrier status; it found that there are limitations associated with this method. These were mainly due to the difficulty in distinguishing between different genotypes and identifying specific gene mutations, all of which are known causes of SMA. The concern was raised that if reliable screening methods were not identified, it may not help health professionals offer advice to assist with reproductive decision making.

    - Evidence regarding the clinical effectiveness of SMA screening was scarce, with no RCTs and only a small number of population-based studies on this topic.

    - There were concerns about the inability of tests to predict the severity of the disease since this could substantially impact the prognosis for a child.

    - No effective or curative treatments for SMA of any type were identified.

4. The 2018 evidence summary was undertaken by Costello Medical, in accordance with the triennial review process. https://legacyscreening.phe.org.uk/sma

5. The 2018 evidence summary addresses questions relating to carrier screening in the general and antenatal populations and newborn screening for SMA. The questions were generated by uncertainties and lack of evidence identified in the previous review. The aims are to assess whether the volume and direction of the evidence produced since the 2013 UK NSC review is sufficient to reconsider the current UK NSC recommendation on screening for SMA.

6. The conclusion of the 2018 evidence summary is that carrier screening for SMA in the general adult and pregnant populations should not be recommended, and that a newborn screening programme should not be introduced at this point in the UK. These recommendations were made on the basis that:

    - In line with the findings of the previous review, there is still insufficient information about the total number of people affected by SMA, or how many people are affected by each type of SMA (and in consequence what level of severity) in the UK. Only one study was identified by this review update. Although this was a large study the evidence base remains limited. The study was generally well-designed; however, there were a number of limitations due to uncertainties on how the data were reported by the laboratories and the type of test used. This study reported an incidence of 10.9 cases per 100,000 live births, which is not consistent with the incidence of 1 in 24,119 births (calculated as 4.15 per 100,000 births) reported by the study from north-east England identified in the previous UK NSC review.
      Criterion 1 not met

    - The sensitivity and specificity of both carrier screening and neonatal screening tests was reported to be high. However, in relation to carrier screening the evidence base was overall weak. The risk of bias was generally unclear, particularly in relation to the reference standards used. There was high concern about the applicability of the included studies to the review question, because SMN1 copy number is not an adequate method for identifying all carriers of SMA. There was also concern regarding the applicability of the populations in each study, since they were not evaluating screening studies in a randomly recruited population.

Similarly, the evidence on tests for newborn screening was weak. Overall, the evidence base had a high or unclear risk of bias and it was based on small population screening studies, in populations that might not reflect the general population. As such there may be biases in the sensitivity and specificity values reported. **Criterion 4 not met**

- This evidence summary found inconclusive evidence on the efficacy on treatment for SMA on the use of olesoxime, while the evidence suggested that valproic acid and somatropin are not effective treatments. **Criterion 9 not met**

- This evidence summary found some promising results suggesting that nusinersen, which is marketed as Spinraza™, 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 is limited with studies still ongoing, and therefore, there is a lack of data for the long-term effectiveness and safety. **Criterion 10 not met**

- There is 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 are unclear. **Criterion 11 not met**

Consultation

7. A three month consultation was hosted on the UK NSC website. Direct emails were sent to 11 stakeholder organisations. **Annex A**

8. Comments were received from the following seven:

   i. Royal College of Paediatrics and Child Health
   ii. Muscular Dystrophy UK
   iii. TreatSMA
   iv. AveXis (Novartis)
   v. Spinal Muscular Atrophy Support UK and The SMA Trust
   vi. Genetic Alliance UK
   vii. Biogen Idec Ltd.

9. The following themes were reflected across stakeholders' comments:

- Several stakeholders suggested that a lack of data on the prevalence in the UK should not be a reason to delay the introduction of a national newborn screening programme.

  Response: Prevalence data and information on the distribution of SMA subtypes is an important part of an evaluation of screening. However the decision on recommending a new screening programme is not based solely on the availability of evidence for a single UK NSC criterion. Instead, the evidence summary covers the evidence on multiple criteria to inform the UK NSC recommendation.

  In relation to the lack of data on the prevalence of SMA in the UK, a stakeholder noted that information on the prevalence of the condition could be available in the near future from National Congenital Anomaly and Rare Disease Registration Service (NCARDRS)

- Several consultees noted that SMA is caused by mutations of the SMN1 gene present on chromosome 5q. In approximately 96% of cases, the condition is caused by the homozygous absence of exons 7 & 8 in the SNM1 gene. The remaining cases result from various point mutations. They suggested that 5q SMA should be the only form of SMA considered as part of the review (i.e. forms of SMA not associated with SMN mutations should not be assessed within the scope of the review), and therefore, any limitations reported in the review associated with non-5q forms of SMA should not be included.

  Response: The authors of this evidence summary propose making this change to the 2018 evidence summary, to focus the questions (and all subsequent interpretation of evidence) on screening for 5q-linked SMA, i.e. SMA that is related to the SMN1 gene on chromosome 5. Although other forms of SMA also result in similar symptoms (e.g. muscle weakness), at the genetic level these are distinct conditions with varied genetic causes and inheritance patterns. The overall suggestion is to state this approach in the introduction to the report and acknowledging it as a limitation to the scope of the review as a whole. This would strengthen the applicability of a number of included studies to the more focused review question.

With respect to the first review question on the epidemiology of SMA in the UK, which is currently not specifically exploring only chromosome 5q will not require amendment as it would be of value to understand the prevalence of SMA overall and the proportion caused by mutations in genes other than SMN1.

- Some stakeholders disagreed with the suggestion that some forms of SMA "do not require treatment", and suggested it is reasonable to expect that in the UK clinical guidance will provide indication on when to commence treatment in milder forms of the condition. However, some stakeholders noted that there are significant ethical implications and dilemmas posed by newborn screening for SMA. This is especially heightened by the use of treatment such as nusinersen, which is involves the administration of the drug via lumbar puncture and requires further life-long treatment once every four months.

  Response: Currently in the UK there are no national clinical guidelines on the management of SMA. However, the latest consensus statement for the diagnosis and management of SMA published in 2007 (updated in 2018) acknowledges that promising results of treatments for SMA are becoming available and in the next few years the scenario is likely to change. In addition, the review point out that currently the screening tests are not able to predict phenotype, therefore, it is unclear which patients should be treated and which not following screening .

- Some consultees suggested that there is evidence available that treatment administrated pre-symptomatically is more effective than treatment after symptoms develop. Similarly, others suggested that there is evidence on the long-term effectiveness of nusinersen in SMA for infantile (type 1) and later onset (type 2/3) patients.

  Response: at the time of the searches for this review no eligible published literature was found on the effectiveness of pre-symptomatic treatments or on long-term effectiveness. Any studies published after the search cut-off will be evaluated by the next UK NSC evidence review update according to the UK NSC evidence review process https://www.gov.uk/government/publications/uk-nsc-evidence-review-process.

There are ongoing trials (for example, NURTURE which is expected to complete by 2022) focusing on treating infants with genetically diagnosed, pre-symptomatic SMA to prevent degeneration before it begins. However, none of these studies have yet reported on the long term efficacy or safety of nusinersen.

- There were concerns about the methodology used by the review and biases in the interpretation of the evidence; including the fact that, perhaps, for screening programmes on orphan or rare conditions, different standards should be used in their evaluation of the evidence and that the methodology used by the UK NSC is much more limiting than the methodology used by other bodies across the world, including the US Food and Drug Administration (FDA), the EMA, the SMC and NICE.

  Response: As for other rare conditions the UK NSC review process was followed in this review. The evidence review process used by the UK NSC reviews is published on the GOV.UK webpage and is available to the public https://www.gov.uk/government/publications/uk-nsc-evidence-review-process.

  UK NSC evidence summaries are developed using rapid review methodologies. They provide an evaluation of the 'volume and direction' of the literature on a single question or set of questions on a given screening topic. They consider whether there have been any significant developments in the evidence base relating to key issues identified from the previous review. Their function is to make a judgement on whether the current recommendation should be retained or whether further work is required.

- Some consultees raised issues relating to the phraseology and content of the review, interpretation of individual papers and overall analysis. Consultees also suggested that some papers had been missed.

  Response: These suggestions were considered by the reviewer and alterations were made to the evidence review where appropriate. Where studies were published within the timeframe of the literature search the reviewer and advisers were asked to consider them for inclusion. None of the papers suggested met the inclusion criteria and were not included in the review. Papers published after the review search dates were not included in the review.

10. All comments are in **Annex B**, below.

Recommendation

11. The Committee is asked to approve the following recommendation:

    Systematic population screening for spinal muscular atrophy is not recommended as a population screening programme in the UK.

Criteria (only include criteria included in the review)	Met/Not Met
Section 1 - Criteria for appraising the viability, effectiveness and appropriateness of a screening programme	
The Condition	
1. The condition should be an important health problem as judged by its frequency and/or severity. 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	**Not Met**
The Test	
4. There should be a simple, safe, precise and validated screening test.	**Not Met**
The Intervention	
9. There should be an effective intervention for patients identified through screening, with evidence that intervention at a pre-symptomatic phase leads to better outcomes for the screened individual compared with usual care. 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 shouldn't be further considered.	**Not Met**
10. There should be agreed evidence based policies covering which individuals should be offered interventions and the appropriate intervention to be offered.	**Not Met**
The Screening Programme	
11. 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" (eg. Down's syndrome, cystic fibrosis carrier screening), 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.	**Not Met**

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Annex A

List of organisations contacted:

1. Biogen
2. The British Society for Human Genetics
3. Faculty of Public Health policy team
4. Muscular Dystrophy Campaign
5. Royal College of General Practitioners
6. Royal College of Paediatrics and Child Health
7. Royal College of Physicians
8. Royal College of Physicians and Surgeons of Glasgow
9. Royal College of Physicians of Edinburgh
10. SMA Trust
11. Spinal Muscular Atrophy Support UK

From the Royal College of Paediatrics and Child Health

Name:	Dr MP Ward Platt	**Email address:**	XXXX XXXX
Organisation (if appropriate):	National Congenital Anomaly and Rare Disease Registration Service (Public Health England)		
Role:	**Consultant Paediatrician (Neonatal Medicine)**		

Do you consent to your name being published on the UK NSC website alongside your response?

Yes ☒ **No** ☐

Section and / or page number	Text or issue to which comments relate	Comment *Please use a new row for each comment and add extra rows as required.*
P 6 and others after	Establishing prevalence	The review notes a twofold variation in prevalence estimates for the UK. It will clearly be important to establish at least the birth prevalence of each type of SMA. NCARDRS is well placed to do this.
P 57	"Without large, prospective studies of SMA epidemiology in the UK population it is not possible to determine the possible impact of a population screening programme."	The national surveillance of the English population by NCARDRS will enable accurate prevalence data to become available within the next year or two.

From Muscular Dystrophy UK

Name:	Clare Lucas	**Email address:**	XXXX XXXX
Organisation (if appropriate):	Muscular Dystrophy UK		
Role:	Campaigns and Engagement Manager		

Do you consent to your name being published on the UK NSC website alongside your response?

Yes ☒ **No** ☐

Section and / or page number	Text or issue to which comments relate	Comment *Please use a new row for each comment and add extra rows as required.*
Page 11	Disease background and burden	As a charity, we support newborn screening in order to get patients with SMA access to emerging treatments, such as nusinersen, as quickly as possible before the condition progresses. SMA is a complex, rare inherited neuromuscular condition that affects the lower motor-neurons in the spinal cord. It leads to the gradual loss of the ability to walk, crawl, move, breathe and swallow. It is a condition that requires complex medical support and is the leading genetic cause of death in infants. Type 1, the most severe and also most common, leads to 80% of affected children dying before the age of 2. Type 2 and 3 still result in significant muscle weakness and disability: Type 2 patients never walk and many Type 3 patients will lose the ability to walk.

		Children require help with washing, dressing, toileting, transferring, eating / drinking. Chest weakness and lung underdevelopment can result in serious respiratory symptoms, such as infections, a weak cough and sleeping problems due hyperventilation. These respiratory issues necessitate constant vigilance and care due to the increased risk of aspiration which can be life threatening. Night care is needed for many people with SMA and parents provide almost all unpaid care. Paid care packages to help parents and families for children range from 0 to 40 hours / week and for adults, from 0 to 70 – 90 hours / week. However, finding and coordinating good paid carers is extremely challenging. The financial impact on affected families is considerable due to expenditure on specialised equipment, adaptations and support. There are also some serious psychological effects of living with SMA, as identified by patients and carers. These include; confronting premature death, difficult treatment choices, fear at loss of function abilities and coming to terms with lost expectations. We feel all of the above needs to be considered when discussing the condition and make decisions on the potential utility of a screening programme.
Page 11	"…there can be a large degree of overlap between SMA types and each type can have highly variable symptoms and prognosis"	We strongly believe that "Type" of SMA should not be the determining factor in whether or not a patient receives treatment. We agree that there is a broad spectrum across each type and the boundaries between types can be blurred. For example, some stronger type 1s currently accessing nusinersen on the Expanded Access Programme are now sitting up - clinically speaking, this would now make them a type 2.

		As such, the fact that screening cannot determine “Type” should not be a determining factor in decision making as we know that the earlier treatment is given the more effective it has been seen to be. The key factor is that appropriate support, including counselling, is available to families going through the screening process.
Page 14	Section around treatments and nusinersen	As a charity, we support many people with SMA who are currently being denied treatment. Nusinersen is the first and currently only treatment for people with spinal muscular atrophy, which is a devastating and progressive condition. We strongly believe that this treatment should be made available to those that would benefit from it, on the basis of clinical decision making. Nusinersen has been shown to have positive, potentially life-changing and life-saving results, something recognised within the recent appraisal consultation document from NICE. The treatment improves not just longevity but also motor function, including respiratory function. It also represents a bridge to emerging treatments for people with SMA. Without access, the condition will be left untreated and people’s health and independence will progressively decline. From the currently available evidence we know that nusinersen is particularly useful at the earliest stages suggesting it could be more appropriate to prioritise treatment for children at diagnosis and pre-symptomatic children. This relies on early diagnosis. Symptoms for Type 1 are within the first few months of live and sometimes before birth, whereas symptoms for Type 2 and 3 are usually seen from 7-18 months. A screening programme could enable children to get access to treatment earlier and therefore

		experience greater health benefits.
Page 15	Carrier screening	We firmly believe that any consideration of implementing carrier screening must be looked at in conjunction with adequate support to help parents make an informed decision.
Page 17	Ethical implications	We recognise the complex ethical implications and questions raised by screening, particularly pre-natal, for families, patients and clinicians. A risk/benefit analysis should take place considering that a treatment is now available and evidence shows that the earlier the treatment is given the more effective it can be for patients. The focus should be on equipping people with the knowledge to enable them to access available treatments and support at the earliest opportunity.
Page 20	Lack of evidence regarding screening effectiveness	This was also a point raised in the last review. We would ask what the committee is doing to gather more evidence? We know that earlier this year the USA approved the recommendation that newborn screening for spinal muscular atrophy be implemented Food and Drug Administration approval of nusinersen. We would strongly urge the committee to reconsider screening at the earliest opportunity is nusinersen becomes more widely available in the UK following the NICE appraisal of the treatment as know that an access agreement is being discussed.
Page 20	Patient education and genetic counselling	We agree with the point that a very considered and consistent approach needs to be adopted around patient education and genetic counselling, if a programme was to be considered, in order to address some of the ethical implications raised by

		screening. The introduction of a screening programme would have clear implications for treatment and life decisions, as well as the longer-term support individuals would need. It is vital that individuals and families are given adequate time and impartial support when making such decisions.
Page 33-35	Epidemiology of SMA	Integrating information on rare diseases is important as there is only a limited amount of data from patients with these diseases. At present most of the data that is collected on SMA patients in the UK is held within two national databases: the UK SMA Patient Registry and the Smartnet database. The UK SMA Patient Registry is a database of genetic and clinical information about people affected by SMA. It is patient reported and one of its main aims is to speed up the process of finding patients eligible for SMA clinical trials. The Smartnet database holds longitudinal data collected by clinicians at routine clinic appointments. SMA REACH UK, an evolution of the Smartnet database, is research project that will continue to collect longitudinal clinical data and will pilot new physiotherapy assessment tools in SMA. The key people involved in these databases have explored an opportunity to collaborate. Data will continue to remain separate in each database but the introduction of a portal will allow the exchange of anonymised information about patients including diagnosis, medical assessment and management of SMA. The aim is to enable better preparation for clinical trials and to bring together in one place accurate details about SMA and how the condition changes over time. This will be jointly managed by the Dubowitz Neuromuscular Centre and MRC Neuromuscular Centres in London and Newcastle.


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From TreatSMA

Name:	Kacper Rucinski	**Email address:**	XXXX XXXX
Organisation (if appropriate):	TreatSMA		
Role:	Board Member		

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Yes ☒ **No** ☐

Section and / or page number	Text or issue to which comments relate	Comment *Please use a new row for each comment and add extra rows as required.*
13	The genetic factors implicated in SMA are complex and vary between types of the disease. Up to 95% of all cases of SMA, however, can be attributed to a homozygous deletion of the SMN1 gene in exons 7 and 8. Other possible causes include a mutation in SMN1 that converts the gene into an SMN2-like gene (known as "gene conversion"), or a trait known as "compound heterozygosity" where one copy of SMN1 is deleted and the other has a mutation leading to loss of function.	SMA is a monogenic disease and the genetic factors implicated in SMA are identical across the entire spectrum. Classification into disease types, while useful in a clinical setting, only weakly correlates with genetic factors. All cases of SMA result from loss-of-function mutations in both the telomeric and the centromeric copy of the SMN1 gene. Around 96% of cases result from exon 7 deletion, the remaining cases result from various point mutations (including the mutation leading to SMN1 ◊ SMN2 gene conversion). About intronic mutations in SMN1, see below.
18	"However, one implication could be the risk of a false	It is proposed in the world that a confirmation of the SMA diagnosis using a different testing method (MLPA) will be

	positive test and the impact this may have on families and the initiation of any unnecessary treatment."	mandatory prior to even informing the family (Glascock, 2018). The probability of a false positive in both tests simultaneously is extremely low. Furthermore, the (relatively low) risk of a false positive does not outweigh the benefit resulting from early introduction of pharmaceutical treatment and multidisciplinary care
19	"Newborn or antenatal tests also have limitations. In particular, there is a risk of overdiagnosis, which is the diagnosis of a condition that would not have caused symptoms during an individual's lifetime."	Asymptomatic homozygous deletion in SMN1 is extremely rare; only a handful of cases have been detected globally in large screening studies (Cobben, 1995: four patients; Hahnen, 1995: seven patients; Prior, 2004: two patients; Wang 1996: 14 patients). The percentage of a patient's family members who have asymptomatic SMN1 deletions is estimated at just 0.5–0.7% (Jędrzejowska, 2011). Further epidemiological data in this topic area can only be gathered through the introduction of routine newborn screening and follow-up.
19	"Individuals carrying a fetus diagnosed with SMA may choose to terminate the pregnancy even though it is unclear how severe the disease would be in the child."	Irrelevant. This is a consultation on newborn screening.
19-20	"For example, some individuals with homozygous deletions or gene conversions in SMN1 are unaffected by SMA symptoms, due to adequate expression of SMN protein encoded by SMN2."	As above. As a general note, case studies, as much as they make for an interesting reading, should never form the basis of a national policy, which should instead be based on universally accepted secondary and tertiary research.
20	"Secondly, a newborn diagnosed with SMA may be treated immediately after birth with invasive treatments such as nusinersen, which is administered via spinal injections, although without treatment they may only have developed a mild form of the disease that did not require treatment."	A suggestion that there exist forms of SMA that "do not require treatment" is unfounded and not based on evidence. To the contrary – there is strong evidence that nusinersen treatment brings about clinically significant (trial data) and patient-relevant (Rouault, 2017) benefit also in the milder forms of the disease. Furthermore, intrathecal drug administration is a routine

		procedure that is carried out safely and with negligible risk of side effects in a number of conditions, including paediatric conditions (cancer, epilepsy) as well as routinely during childbirth (epidural anaesthesia). In nusinersen therapy, the procedure is done once every 4 months; while the investigational drug AVXS-101 requires a single administration. The suggestion that the burden of IT injections exceeds the burden resulting from the natural course of SMA is a grave misunderstanding (Klug, 2016; Farrar, 2018). Finally, the assumption that treatment will always be introduced "immediately after birth" is baseless. Specifically, the US treatment algorithm for infants diagnosed through newborn screening mandates observation instead of treatment in newborns with four or more SMN2 copies (Glascock, 2018). In the UK, it is reasonable to expect that the relevant guidance will mandate initiation of treatment only at the onset of subclinical symptoms (e.g., early tongue fasciculation or reduced ulnar CMAP), i.e., well before clinical signs of irreversible neuronal and muscular damage prompt the diagnostics as is the case currently.
19	An additional risk is that antenatal screening may also detect women who are developing or will develop late-onset SMA, which may lead to additional anxiety during pregnancy"	Unclear sentence. Also, a proposition that the burden of anxiety should outweigh the burden of having a child with a probably fatal disorder is unacceptable to us
30	"Moreover, the study only considered SMA caused by SMN1 mutations, and did not look at other cause of SMA other than SMN-related mutations. Therefore, these remaining patients will not have been captured in the incidence calculations, which may lead to an underestimation of the true incidence of SMA. These	Irrelevant. This is a consultation on newborn screening in 5q spinal muscular atrophy, a disorder always related to a lossof-function mutation in the SMN1 gene. We assume throughout that this consultation does not cover other similarly named disorders, e.g., spino-bulbar muscular atrophy, sometimes called "X-linked spinal muscular atrophy type 1" (NR3C3 gene); arthogriposis

	limitations make it difficult to assess the extent to which the evidence is applicable to the general UK population."	multiplex congenita type 1, sometimes called "X-linked spinal muscular atrophy type 2" (UBA1 gene); or various "distal spinal muscular atrophies", or distal hereditary motor neuropathies, which are linked to several other genes. Therefore, identifying a study on 5q SMA (i.e., Verhaart, 2017) for this review and complaining that it does not include disorders outside of scope of this review is somewhat baffling. Consequently, the conclusion that "Criterion 1 was not met" is associated with a profound methodological problem
35	"This study reported an incidence of 10.9 cases per 100,000 live births, which is not consistent with the incidence of 1 in 24,119 births (calculated as 4.15 per 100,000 births) reported by the study from north-east England identified in the previous UK NSC review. Although the current study is larger, the unclear methodology means that it is uncertain whether this finding is a more accurate estimation of the incidence of SMA in the UK."	The discrepancy between the 1978 and 2017 studies is incorrectly held against the latter study. Actually, UK SMA registry data indicates that SMA incidence and prevalence in the North, in Wales and in Northern Ireland is significantly lower than elsewhere. Additionally, the 1978 study was carried out well before molecular basis of SMA was understood, genetic testing was introduced and several other non-5q disorders resembling SMA were discovered. In our view, this old paper should be discarded altogether because a newer study has brought about more detailed, nationwide data on 5q SMA epidemiology. Par analogiam, Verhaart 2017 allows the Criterion 1 to be fulfilled.
36	"SMN1 de novo mutations, which occur in approximately 2% of SMA patients (1% of parents) would not be detected"	De novo (non-inherited) mutations are normally detectable using standard testing methods.
44	"However, SMN1 exon 7 deletion is not the only known genetic cause of SMA. A homozygous deletion of SMN1 exon 7 is thought to cause 95% of SMA cases, so screening for these deletions alone would not identify all participants with SMA. These high clinical	A loss-of-function mutation in SMN1 is responsible for at least 96% of cases of SMA, possibly significantly more. Yes, there exist case reports of intronic mutations leading to the SMN1 loss of function which are not detectable using standard PCRRTFL or MLPA; however, their occurrence seems marginal.

	performance results should be interpreted with some caution as they are not a true measure of SMA identification."	
46	Entire chapter	Out of date in view of the 2018 publications on standard of care (Mercuri, 2018; Finkel, 2018)

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Please return to the Evidence Team at screening.evidence@nhs.net **by 9th September 2018**

From AveXis (Novartis)

Name:	XXXX XXXX	**Email address:**	XXXX XXXX
Organisation (if appropriate):	AveXis		
Role:			

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Yes **No X**

Section and / or page number	Text or issue to which comments relate	Comment *Please use a new row for each comment and add extra rows as required.*
5	SMA is an autosomal recessive disease, the second most common of this kind after cystic fibrosis	SMA is a rare, fatal and rapidly progressing neurological disease. Not only is SMA the second most common disease after cystic fibrosis but SMA Type 1, the most common form of SMA, is the leading genetic cause of infant death in infants[1]. Over 90% of SMA Type 1 patients die or require permanent ventilatory support by the age of 2 years and do not achieve any developmental milestones[2]. The clear evidence of the burden of disease should ensure all countries very carefully evaluate not only 'if' the disease should be systematically screening for but describing 'how' the disease can be accepted for screening within the country.
5	Most cases of SMA (95%) are caused by mutations in	SMA is caused by mutations of the SMN1 gene present on

	survival motor neuron (SMN)* genes, which code for the SMN protein. The vast majority can be attributed to a homozygous deletion of the SMN1 gene in exons 7 and 8. Other possible causes include SMN1 mutation, or "compound heterozygosity" where one copy of SMN1 is deleted and the other has a mutation leading to loss of function.	chromosome 5q. In approximately 96% of cases, SMA is caused by the homozygous absence of exons 7 & 8 in the SNM1 gene. In 3-4% of cases other mutations in SMN1 can be found, typically with an SMN1 deletion on the other allele[4]. These cases are normally due to intragenic subtle SMN1 mutations[3]. SMA is a genetic disease with distinctive, well known pathophysiology indicating the possibility of screening programs to detect cases from the general population. Almost all cases will be systematically detected by screening programs and given the fatal and rapidly progressive severity of the disease and the burden imposed to patients and families, it is crucial to implement screening to ensure early detection.
5	In the UK, there are currently no approved, disease-modifying treatments for SMA and current management involves a holistic approach to disease symptoms. However, the Food and Drug Administration (FDA) in the US and the European Medicines Agency (EMA) in Europe recently approved nusinersen (SpinrazaTM), an antisense oligonucleotide (ASO)† for the treatment of both mild and severe SMA.	Due to the mid/long-term nature of UK NSC reviews it is important to not only assess the current approval landscape today but indeed the horizon scanning and pending evaluation of treatments which may have the possibility to positively alter the natural history of SMA following early detection. In your assessment, further in the document, you mention there is an 'Early Access Program' in place for nusinersen, providing access to therapy for patients and to quote: "all infants diagnosed with SMA type 1 before 7 months will be treated". This program should not be disregarded as it is available and is facilitating SMA patients to be treated in the UK today. This should be taken into scope during the evaluation. There is also well established and accepted standards of care (SOC) providing the possibility of improved care to patients, especially when diagnosed early.

		We call on the UK NSC to be pragmatic to ensure SMA patients do not fall behind the diagnostic and care options offered to patients in other countries.
7	The review found no effective treatments and no cure for SMA of any type; however, the first consensus statement for SMA in 2007 was identified, which recognised management of the symptoms of SMA as the current standard of care.	In 2017 SMA experts published further consensus care guidelines as an update to the 2007 guidelines. These is widely recognised as best care guidelines for SMA[4]. Also note; the points above regarding 'no effective treatments'.
7	Concerns about the inability of antenatal and neonatal tests to identify the severity of the disease were also discussed as this could substantially impact the prognosis of an affected individual.	The International Standard of Care Committee for SMA developed a consensus-based stepwise algorithm of the diagnosis of SMA[4]. The gene deletion test that could be utilised for newborn screening has up to 95% sensitivity and nearly 100% specificity. Upon identifying homozygous deletions in SNM1, further testing of the SMN2 pseudogene copy number allows for prediction of the expected course of disease[5]. SMN2 should be routinely assessed after a diagnosis of SMA as it is an important factor influencing the severity of the SMA phenotype[5].
9	There is also a lack of evidence on the relationship between SMA genotype and clinical prognosis	Please see the above point. Additionally, as a screen, SNM1 is highly sensitive and specific. Upon referral for diagnosis it is best practice and routine to conduct testing of SNM1 and further qPCR or MLPA testing of SMN2 in order to assess the copy number which is a well understood marker for SMA severity.
8	Two studies found that mCOP-PCR and HRM analysis are highly sensitive and specific newborn SMA screening methods. However, these methods identify	Screening tests for SMA are highly sensitive and specific[4]. In approximately 96% of cases, SMA is caused by the homozygous absence of exons 7 & 8 in the SNM1 gene. In 3-4% of cases other

	SMN1 exon 7 deletion, which is not the only underlying cause of SMA.	mutations in SMN1 can be found, typically with an SMN1 deletion on the other allele[4]. In the US, the Recommended Uniform Screening Panel (RUSP) is a standardised list of disorders that have been supported by the Advisory Committee on Heritable Disorders in Newborns and Children (ACHDNC) and recommended by the United States Secretary of Health and Human Services (HHS) for inclusion in state universal NBS programs. Disorders added to the RUSP are based in evidence supporting the potential net benefit of screening, the ability of states to screen for the disorder, and the availability of effective treatments. In February 2018 the ACHDNC decided in favour of adding SMA to the newborn screening panel. It was subsequently accepted by the Secretary of Health and Human Services and is now being implemented across many of the States. Other countries across Europe are also making strong progress to validate and evaluate the potential of adding SMA to newborn screening. For example; Newborn Screening in Belgium to demonstrate the feasibility, medico-economic impact of SMA neonatal screening in a European country[6]. We call on the UK NSC to be pragmatic to ensure SMA patients do not fall behind the diagnostic and care options offered to patients in other countries.
9	Overall, the evidence base on the epidemiology of SMA is still limited	The epidemiology of SMA is very well documented. The prevalence of SMA is estimated at 1 to 2 per 100,000 persons

		and the incidence is estimated at ~1:10,000 live births[7,8]. For UK specific data, there is a UK SMA registry in place. This registry was set up in 2008 as a collaboration between Spinal Muscular Atrophy Support UK and Treat-NMD Neuromuscular Network. It is part of a global SMA registry and as of 23rd August 2018, it reports 666 SMA patients in the UK registry[9]. The investigator in charge is Professor Hanns Lochmüller from Newcastle. We encourage the UK NSC to engage with healthcare professions and support groups in the UK to fully understand the known epidemiology and the real-world evidence of SMA in the UK.
10	No evidence was found evaluating the outcomes of different screening programmes for carrier status and newborn screening. Interventional and prospective observational studies are therefore needed to evaluate the effectiveness and impact of such screening programmes.	As previously mentioned, many countries have started the process of assessing the feasibility of SMA for inclusion in newborn screening and it is vital UK patients do not get left behind. In the USA, a population-based newborn screening study demonstrated the feasibility of screening, the acceptance by families and the benefit of newborn screening for SMA patients[10]. Subsequently, SMA is now being implemented in screening programs across the USA. Furthermore, a team from the National Taiwan University Hospital evaluated and published Presymptomatic diagnosis of SMA through newborn screening and concluded screening can detect patients before symptom onset and enable early therapeutic intervention by accurately diagnosis SMA from dried bloody spot samples with no false-positives[11].

		SMA is a rare, fatal and rapidly progressing neurological disease. Not only is SMA the second most common disease after cystic fibrosis but SMA Type 1, the most common form of SMA, is the leading genetic cause of infant death in infants[1]. There is currently a significant delay in the time to diagnosis of SMA. According to a systematic literature review, the diagnostic delay was 3.6 months, 14.3 months and 43.6 months respectively for SMA types I, II and III[12]. Further underlining the importance of screening in newborns for this devastating disease.
16	At the present time, antenatal screening involves invasive procedures to gather fetal DNA, followed by genetic analysis in the form of restriction fragment length polymorphism (RFLP) testing, multiplex ligation-dependent probe amplification (MLPA) or quantitative polymerase chain reaction (qPCR).	Non-invasive prenatal diagnosis (NIPD) of SMA was recently published in the UK demonstrating high specificity and sensitivity[13].
17	there is currently no clear consensus on the impact of parents receiving the news that their child is affected by SMA at birth, through newborn screening programmes	Boardman F et al have published specifically in the UK on the views of affected families and adults of newborn screening for SMA underlining that the majority (70%) were in favour of newborn screening, with other groups preferring pre-conception or prenatal screening[14]
20	A previous review was conducted for the UK NSC in 2013, with the aim of summarising the available evidence concerning screening in SMA.	It is important to note that newborn screening was not within the scope of the 2013 review or the previous literature search. Literature searches also only include peer-reviewed publications. It should also be mentioned that the field of SMA is rapidly evolving, hence the screening landscape for SMA is being reviewed in many countries in order to detect and provide the optimum care in both standard of care and therapeutic options for patients and families.

		We call on the UK NSC to be pragmatic to ensure SMA patients do not fall behind the diagnostic and care options offered to patients in other countries. We request that the topic of screening for SMA, in particular for newborn screening, be revaluated within the short term to ensure the UK stays abreast of this changing landscape and in line with other countries who are offering or plan to offer the detection of this serious, progressive and high morbidity and mortality disease in the general population.

[1]Kochanek 2016/p98/tbl21; Murphy 2017/p54/tbl_14
[2]Finkel 2014/p813/fig_1C
[3]Alias 2009/p30A
[4]Mercuri E 2017, neuromuscular disorders 2018Feb;28(2):103-115
[5]Anderton2015, Feldkotter2002
[6]https://clinicaltrials.gov/ct2/show/NCT03554343
[7]Ogino 2002/p303/col2para2
[8]Verhaart 2017/a/p2/col2/para4, p5/col1/para2, p5/col2/para5, p8/col1/para4
[9]https://www.treat-nmd.org.uk/registry
[10]Kraszewski J, Genetics in medicine, Vol20/number6/June 2018
[11]Chien YH. Jpeds2017.06.042
[12]Lin Chia-Wei, Pediatric Neurology 53 2015 293-300
[13]Parks M, Eur J Hum Genet. 2017 Apr; 25(4): 416-422
[14]Boardman F, Am J Med Genet 2017:173A:1546-1561

From Spinal Muscular Atrophy Support UK and The SMA Trust

name:	Liz Ryburn	**Email address:**	XXXX XXXX
Organisation (if appropriate):	Spinal Muscular Atrophy Support UK and The SMA Trust (merging to form Spinal Muscular Atrophy UK)		
Role:	**Support Services Manager**		

Do you consent to your name being published on the UK NSC website alongside your response?

Yes ☐ yes **No** ☐

Section and / or page number	Text or issue to which comments relate	Comment *Please use a new row for each comment and add extra rows as required.*
Page 7.	**Criterion 1, the prevalence of SMA in the UK has not been met following the review update**	We refer to the following studies which were also reviewed by the NSC: • Verhaart I *et al.* (2017) **Prevalence, incidence and carrier frequency of 5q–linked spinal muscular atrophy –a literature review.** *Orphanet J Rare Dis* 12: 124. • Verhaart I *et al.* (2017) **A multi-source approach to determine SMA incidence and research ready population.** *J Neruol* 264: 1465-1473 These conclude: **Prevalence** - between 1 and 2 people in every 100,000 worldwide have a type of 5q SMA. In 2017, the UK population was approximately 66 million. Based on this, it is estimated that between 660 and 1320 people have SMA in the UK at any one time. We are aware that these papers are based on global observations of incidence and prevalence, but until we have an accurate UK-wide register of those born with 5q SMA, and those already living with 5q SMA, we suggest these give the most accurate available data. We note that the NSC is concerned to identify the prevalence of **all** forms of SMA, irrespective of genetic aetiology. However, the NSC's criteria 10 focuses on reviewing

		the effectiveness of pharmacological treatment for SMA. Currently, the only treatment available for SMA (Nusinersen) is exclusively targeted to those with confirmed 5q SMA, which is by far the most common form of SMA. It is therefore the prevalence of 5q SMA that is important when considering whether this condition meets NSC criterion 1. **In summary: we suggest that there is enough global evidence of the prevalence of 5q SMA. If the NSC requires further information about the prevalence in the UK, we ask that they work closely with NICE which is addressing the very same question in its deliberations about whether to recommend the treatment nusinersen for NHS funding (see below). However, if other criteria are met, we ask that any current population uncertainties do not hold up the possibility of progressing a 5q SMA newborn screening programme.**

Page 7.	**Criterion 1 'there is no evidence as to how many people are affected by each type of SMA**	We refer to the above studies, which conclude an **incidence** of 5q SMA of approximately one in every 10,000 babies worldwide. In the UK in 2017, there were 755,043 live births. This suggests that, in that year, approximately 76 babies were born with a Type of 5q SMA. These studies further conclude the incidence of the types of childhood onset SMA:
		
		• **Type 1: 60% infants age < 6 months* – suggesting 46 infants each year**
		• **Type 2: 21% children ages 6 – 18 months – suggesting 16 children each year**
		• **Type 3: 19% children including - suggesting 14 children each year, including:**
		  ○ **Type 3a ages 18months – 3 years**
		  ○ **Type 3b age 3 years plus**
		
		(*we note the NSC review page 11 suggests only 50%)
		
		We acknowledge that the % of type is based on global studies and that there is an urgent need for more work to be commissioned to establish this accurately in the UK context. However, the Expanded Access Programme (EAP) providing nusinersen treatment for those with SMA Type 1 has now been nationally available since August 2017, with children's progress tracked via the SMA REACH project. We understand that some parents of infants diagnosed with SMA Type 1 are declining treatment, but that number is now very small and

		should be known by treating clinicians. This means we are now very close to having much more accurate data on the incidence of this type of SMA in the UK. We have highlighted to NICE that work to establish population numbers and type of SMA is urgently needed if they are to progress a much-needed Managed Access Agreement for nusinersen. We suggest that in the interim, the percentages above, combined with average life expectancy for those with each type of SMA could be a sufficient guide for numbers. **In summary: If other criteria are met, we ask that any current population uncertainties do not hold up the possibility of progressing a 5q SMA newborn screening programme.**
Page 7	**Criterion 1. It is not yet possible to accurately determine from an individual's genotype whether they will be mildly or severely affected by SMA**	**The age of onset of symptoms of 5q SMA and the *SMN1* gene deletion test quickly (2-4 weeks) inform a diagnosis of 5q SMA Type 1, 2, 3 or 4.** **The *SMN2* copy number has also been seen as a potential way of further establishing the future course of the condition. However, the internationally agreed Standards of Care for SMA (2017)[1,2] (SoC) show the narrow variance between the 'usual' number of *SMN2* copy numbers compared with the possible 'range' described by Tillmann *et al*[3]. Those with:** • **Type 1 have a 'usual' *SMN2* copy number of 2 but a 'range' of 1-3 copies** • **Type 2 have a 'usual' *SMN2* copy number of 2 but a 'range' of 2-4 copies** • **Type 3a have a 'usual' *SMN2* copy number of 3 but a 'range' of 3-5 copies** • **Type 3b have a 'usual' *SMN2* copy number of 4 but a 'range' of 3-5 copies** **As stated in the 2017 SoC,** at the individual level, perfectly accurate predictions cannot be made about the type or severity of SMA based on *SMN2* copy number alone. This is due to other genetic and possibly environmental factors that have a small influence on the disease course. **We note, however, that the information about *SMN2* copy number and other tests are considered as sufficient to predict the severity of an infant's 5q SMA when used in**

		newborn screening programmes in the USA (see below) We are aware that there is also significant ongoing research into the predicted future disease impact, which includes both genotype and looking at biomarkers. **1.** Mercuri, E *et al.* (2017) **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. **2.** Finkel, R *et al.* (2017), **Diagnosis and management of spinal muscular atrophy: Part 2: Pulmonary and acute care; medications, supplements and immunizations; other organ systems; and ethics**. Neuromuscul Disord. 2018 Mar;28(3):197-207.) **3. Tillmann, A *et al.*** (2018) **Spinal Muscular Atrophy (SMA) type 1, a changing phenotype: Implications for motor function and physiotherapy management from the Nusinersen Expanded Access Program (EAP)** APCP Journal Volume 9 Number 1)
Page 8	***Criterion 4. There should be a simple, safe, precise and validated screening test.***	The NSC review states that, 'it is not possible to robustly quantify the accuracy of screening methods for SMA neonates' We note that the NSC has evaluated four studies and finds that they provide weak evidence for such a test. Again, these tests are seeking verification of 5q SMA. We note the further study by Kraszewski, J.N *et al.* (2017) **Pilot study of population-based newborn screening for spinal muscular atrophy in New York state** Volume 20 | Number 6 | June 2018 | GENETICS in MEDICINE which reports on **newborn dried blood spot (DBS) screening of** 3,826 newborns screened at three hospitals in New York City from January 2016 to January 2017. They were tested for 5q SMA using the deletion in exon 7 of *SMN1*. We don't know if the NSC would regard this study as

		sufficiently robust given its other critique's, but note that as a result of this study, **one** infant was enrolled in the NURTURE clinical trial (see below) and was first treated with Spinraza (see below) at age 15 days. She is now age 12 months, meeting all developmental milestones, and free of any respiratory issues. **In summary: newborn screening tests are being used to identify infants with 5q SMA. If such testing is introduced it would need to be made clear to parents that the test is for 5q SMA, the most common form of SMA with clear information about the accuracy of the test and that this test does not cover all possible other very rare forms of SMA.**
Page 8.	***Criterion 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.***	As the NSC review points out, the 2007 Consensus statement on the Standards of Care for SMA, subsequently published as the 'International Standards of Care for SMA' have focused on management of the condition. Largely due to the improvements in care and management that they have driven, there's been increasing evidence that people with SMA and their families can expect a better quality of life than in the past. Their recent updating in 2017 capture the many changes there have been in management of the condition and will no doubt be the NSC's reference base in any further base. **Nusinersen treatment** As the NSC review points out, Nusinersen, which is marketed as Spinraza™, is the first disease-modifying treatment for SMA. The review considers the results of Biogen's clinical trials (ENDEAR and CHERISH) showing the positive outcomes of nusinersen treatment in Children with SMA Type 1, 2 and 3. A further trial, SHINE, looking at longer term outcomes is ongoing. The following publications confirm outcomes in 'real world' studies of the nusinersen Expanded Access Programme for SMA Type 1[1-5] All indicate that the earlier the treatment, the greater the benefit:

		1. **Europe -** 33 children aged from 8.3 to 113.1 months - December 2016 - May 2017. **Aragon-Gawinska, K *et al*.** (2018) **Nusinersen in spinal muscular atrophy type 1 patients older than 7 months. A cohort study** Neurology® 2018;00:1-7. doi:10.1212/WNL.0000000000006281 2. **Australia** – 16 patients aged 2.5 months to 35.7 years November 2016 – September 2017 **Farrar, M *et al*.** (2018) **Nusinersen for SMA: expanded access programme** J Neurol Neurosurg Psychiatry 2018;**89**:937–942. doi:10.1136/jnnp-2017-317412 3. **England - Great Ormond Street Hospital** – 21 patients aged 8.3 – 113.1 months March – October 2017 **Tillmann, A *et al.*** (2018) **Spinal Muscular Atrophy (SMA) type 1, a changing phenotype: Implications for motor function and physiotherapy management from the Nusinersen Expanded Access Program (EAP)** APCP Journal Volume 9 Number 1 4. **Germany** – 61 patients aged 1 – 93 months in seven neuromuscular centres November 2016 – June 2017 **Pechmann, A *et al.*** (2018) **Evaluation of Children with SMA Type 1 Under Treatment with Nusinersen within the Expanded Access Program in Germany** Journal of Neuromuscular Diseases 5 (2018) 135-143 DOI 10.3233/JND-180315 5. **Italy** – 104 patients – aged 3 months – 19 years 9 months - first six months of EAP **Pane, M *et al.*** (2018) **Nusinersen in type 1 SMA infants, children and young adults: Preliminary results on motor function** Neuromuscular Disorders 28 (2018) 582-585 30 May 2018 The NSC review refers to results published by Bertini *et al*. in 2017 from NURTURE, the ongoing open-label, single-arm study evaluating the efficacy and safety of nusinersen in pre-symptomatic infants with genetically

		confirmed SMA and comments on the improvements that infants have made, though criticises that the study did not compare pre-symptomatic treatment to treatment after symptoms start. We suggest that this is being addressed through further studies, Biogen's long term follow up clinical trial, SHINE, of all treated with nusinersen to date and the now many 'real world studies of treatment that are ongoing. We note Biogen's March 12th, 2018 summary of the interim Phase 2 results as this model and its outcomes appears to be underpinning the newborn screening programmes that are now operating in the USA: In the NURTURE study, SPINRAZA was administered to infants six weeks old or younger, who were in the pre-symptomatic stage, genetically-diagnosed with SMA and had two or three copies of the *SMN2* gene (n=15 for two copies (most likely to develop Type 1 SMA); n=10 for three copies (most likely to develop Type 2 SMA)). At the time of this interim analysis, infants had been followed for up to 25.6 months – well beyond the typical timeframe when most infants with Type 1 SMA would have required permanent ventilation or died. The interim analysis, showed that all infants were alive, and none required tracheostomy or permanent ventilation. All showed improvement in motor function and motor milestone achievements as of July 5, 2017, compared to the disease's natural history. Dr. Darryl C. De Vivo, M.D., lead study author said, "The NURTURE findings document the continuing benefits that SPINRAZA provides for patients with SMA who initiated treatment in early infancy while clinically pre-symptomatic, including age-appropriate developmental gains in motor function and motor milestone achievements," and "The treated infants in the NURTURE study had genetic SMA and were likely to clinically develop Type 1 or 2, yet with enough observation time they have all achieved

		independent sitting and the majority have developed the ability to walk." NURTURE participants also achieved a mean CHOP INTEND score, which measures general motor function among infants with SMA, of 58.4 at last visit (out of a maximum score of 64). Many continued to improve and maintain these scores beyond a point in time at which untreated individuals with Type 1 SMA would experience a significant decline. Overall, the study showed that SPINRAZA was well-tolerated and no new safety concerns were identified. Though still early on in the study, and without the benefit of a full analysis of how much greater the gains are for these children compared with children who have been followed via the ENDEAR study, results seem to suggest greater efficacy of pre-symptomatic treatment and therefore greater potential cost savings : Finkel, R *et al*. for the **ENDEAR** Study Group (2017) **Nusinersen versus Sham Control in Infantile-Onset Spinal Muscular Atrophy** n engl j med 377;18 nejm.org November 2, 2017 states 'Approximately half the infants in the nusinersen group who received permanent assisted ventilation did so within 13 weeks after they received the first dose; this result indicates that a minimum treatment time is required to see the full benefits of nusinersen. This result, as well as our finding that infants with a disease duration at screening longer than the median duration of 13.1 weeks were more likely than those with a disease duration no longer than the median duration to need permanent assisted ventilation, suggests that early initiation of treatment may maximize its efficacy.' **In summary: there is a growing body of clinical trial and real-world evidence of the effectiveness of nusinersen treatment for 5q SMA and that the earlier the treatment the greater the impact, with strong indications that the greatest impact occurs if it is started pre-symptomatically.** **Other treatments** There are also other treatments on the horizon which are coming close to completion of

		clinical trials and, one imagines, possible applications for licences (**AveXis' AVXS-101, Roche's RG7916 / risdiplam**). **We note that these are also indicating that the earliest possible treatment has the greatest impact.**
Page 9	***Criterion 10: There should be agreed evidence-based policies covering which individuals should be offered interventions and the appropriate intervention to be offered***	**Screening programmes in the USA** In terms of screening of SMA neonates, **we note that several US states have recently introduced newborn screening. Those with between 1 and 3 *SMN2* copies are offered nusinersen treatment and those with 4 *SMN2* copies** (carried by the majority of those with SMA Type 3b) **are monitored.** Newborn screening for 5q SMA is now, we understand, on the Recommended Uniform Screening Panel (RUSP), which makes it much more likely that additional states will adopt it. **In summary: Effective screening programmes for 5q SMA are now operating globally which, as well as the confirmed diagnosis, use information gained from *SMN2* copy numbers to establish which children should be treated and which monitored. These are establishing an evidence-based policy as to which individuals should be offered interventions and the appropriate intervention to be offered.** **Access to treatment in the UK** As the NSC knows, nusinersen treatment has been available in the UK for those with SMA Type 1, via Biogen's global Expanded Access Programme (EAP). Since August 2017, this has been limited to those who are <7 months of age, Biogen has announced that this programme will close on 1st November 2018. On 7th May 2018, Scotland agreed to fund the treatment for those with SMA Type 1. On 18th June 2018, the Scottish Government announced *it is introducing a new definition of 'ultra-orphan medicines' that can treat very rare conditions affecting fewer than 1 in 50,000 people - around 100 people or less in Scotland', advising that this would be implemented on 1st October 2018.* Biogen has made it known that it has applied for nusinersen to be the first drug to be appraised for those with SMA Type 2 or 3 via this new system. The NSC also refers to NICE's current appraisal of the treatment. Clinicians, patient and

		parent groups are working hard to respond to NICE's initial report, which does not recommend funding. Clinicians, patient and parent groups are pushing for a reversal of this decision and access for all with SMA Type 1,2 or 3 SMA or, at the very least a Managed Access Agreement. There is currently no clinical trial evidence for treatment of those with the much rarer SMA Types 0 or 4. **In summary: In Scotland an effective treatment, nusinersen, is available for those with SMA Type 1. We await the possibility of this being extended to those with Type 2 or 3. We also await the outcome of NICE's decision making as to who will be eligible for treatment in England and Wales. This should be finalised by 21st November 2018. We understand Northern Ireland may follow either Scotland or England.** There is growing clinical evidence that a newborn screening programme will be essential for ensuring greatest potential benefit from nusinersen treatment and, in due course other treatments. This screening programme would identify children who will develop SMA Types 1, 2 or 3. which will allow the earliest possible monitoring and best possible management based on the SoC. However, unless treatment is available to all these children, it will lead to unimaginable distress for families. NICE and the Scottish Medicines Consortium and the NSC must coordinate their thinking and planning. **In summary: at this stage it is not known which children will be able to access nusinersen treatment in the UK. This decision and the possible criteria for a proposed screening programme are critical to any further debate and decision making**
Page 17.	**Ethical implications and dilemmas**	**We note and agree there are considerable ethical implications and dilemmas posed by newborn screening. This includes whether it should be an opt in or opt out programme. Furthermore, current screening programmes for 5q SMA will, we imagine, also potentially identify those who will at some point in their lives develop adult onset Type 4. The current method and life-long delivery required for nusinersen would not be an option. Though screening offers the possibility of monitoring, creating a scenario whereby families has to live with this knowledge creates significant ethical challenges.** **In summary: any screening programme must be accompanied by a robust and ongoing programme of supportive counselling and accurate information about: what information**

<table>
<tr><td></td><td></td><td>may be revealed via the screening test; what impact the various types of 5q SMA have on life; what management and treatments are available.</td></tr>
<tr><td>Page 17</td><td>SMA Community Views – do people want access to nusinersen?</td><td>In January 2018 we conducted a survey about the impact of SMA on children, adults and their families. We also asked for views on access to nusinersen.

The responses of parents/carers to the question ‘Would you want your child to have access to nusinersen?’ is most relevant to this submission. Respondents were aware that the treatment would involve repeated lumbar puncture deliveries over the person’s lifetime and that long-term outcomes were not known.

56 parents/carers responded. 95% said yes, they would want their child to have treatment, and 5% said no.

Of those that said yes, their child had the following SMA Type and is the age shown below:

<table>
<tr><td>SMA Type</td><td>1</td><td>1 / 2</td><td>2</td><td>2 / 3</td><td>3</td></tr>
<tr><td>%</td><td>4</td><td>60</td><td>2</td><td>32</td><td>2</td></tr>
<tr><td>Age (years)</td><td>0-2</td><td>3-4</td><td>5-12</td><td>13-17</td><td>18+</td></tr>
<tr><td>%</td><td>13</td><td>11</td><td>34</td><td>8</td><td>34</td></tr>
</table>

The 5% that said ‘no’ have children aged 13 – 17 years who have SMA Type 2.

This does perhaps indicate that, even with the uncertainties of long term outcomes and the method and frequency required for delivery of the treatment, it is likely that the uptake for those with children screened for treatment would be very high.

SMA community views – attitudes to newborn screening
We already know from Dr. Felicity Boardman’s work that the SMA community is</td></tr>
</table>

		largely supportive of newborn screening, particularly when compared to other forms of screening that involve the potential loss of SMA lives. • Boardman F*, et al.* (2016). **Newborn screening for spinal muscular atrophy: the views of affected families and adults.** American Journal of Medical Genetics 173A: 1546-1561. Dr Boardman's paper on the views of the general population on newborn screening for SMA indicates that 84% of those surveyed (232) were in support of newborn screening for SMA is also salient: • Boardman, F *et al.* (2017). **Newborn genetic screening for SMA in the UK: the views of the general population.** Molecular Genetics and Genomic Medicine, 1-10. The introduction of nusinersen is likely to only bolster this support as shown by the follow up study we conducted in August 2018 – a survey of community views on newborn screening (survey monkey link sent out via social media and our monthly e-news). As access to nusinersen has been at the top of the agenda for the SMA community this year - focusing on raising awareness with the media and MPs and taking part in NICE's appraisal, it was not surprising that this only elicited 19 responses. However, results were: • 84% of respondents were affected by SMA Type1; 37% were bereaved by SMA Type 1. • 95% strongly agreed that newborn screening should be introduced in the UK, 5% neither agreed nor disagreed.

		• 89% strongly agreed and 11% agreed that it should be a programme similar to ones in the States that offer treatment to those with between 1 and 3 *SMN2* copies and that those with 4 copies of *SMN2* (carried by the majority of those with SMA Type 3b) should be monitored • 84% strongly agreed and 16% agreed that a newborn screening programme that led to the earliest possible treatment would, in the long run, result in better quality of life for children and families Comments included: 'diagnosis took agonising months as local GPs kept fobbing us off. Clearly, they had no idea what was wrong. Screening at birth would alleviate all those months of anguish and better prepare parents for care and treatment.' **Bereaved Grandparent of child with SMA Type 1** 'If we had known sooner then a lot of worry about what was wrong with our child would have been eliminated. Treatment could have started sooner and may have had more impact on our child's progress. xxxx xxxx didn't start until xxxx xxxx was over one year old even though xxxx xxxx has type 1. Our child, if treated earlier, may not now need a peg to be fed or a ventilator at night. xxxx xxxx may have head control like xxxx xxxx once had if diagnosis and then treatment could have started earlier.' 'I think it would allow for planned, more focused treatment rather than emergency trying to investigate symptoms. It also gives families a chance to come to terms and learn about the condition rather than having to do this whilst look after an already sick child. It would also give the various agencies involved more time to create a treatment plan. xxxx xxxx was not diagnosed until a few weeks before xxxx xxxx died. By the time we had our first meeting about treatment options the best one available was to move to a hospice with xxxx xxxx and keep xxxx xxxx comfortable. I think with this condition the amount of time you have before symptoms are obvious are crucial.' **Parent of child with SMA Type 1 receiving treatment**

		'I agree it is a useful tool. However, I feel it should be a choice rather than part of the national screening per se. I didn't know my xxxx xxxx had SMA or that we were carriers. If we'd had more children knowing the risks I wouldn't have screened.' **Bereaved Parent of child with SMA Type 1** 'Screening may cause extra anxieties in the early days of parenthood if parents don't want to know a diagnosis that soon.' **Bereaved Parent of child with SMA Type 1** As someone with SMA (Type II), I strongly believe in newborn screening procedures when it comes to genetic diseases as I think that the information that it provides is far too important to be ignored. Any available chance not taken to improve someone's current/future quality of life, whether via treatment (after considering the risks of said treatment) or just by planning for the future, is a wasted opportunity and, in my own personal opinion, immoral. **Adult with SMA Type 2** **In summary: Evidence to date indicates a high level of support from the SMA community and the public for newborn screening for 5q SMA**
	Our conclusion	**We conclude that a further urgent review of a newborn screening programme for 5q SMA in the UK is imperative due to the development of a life-saving intervention for children with SMA, together with clear evidence from trials that early treatment has a major influence on subsequent functional outcomes, the rapid changes we are seeing with research and the development of other new treatments and the introduction of screening programmes in the USA and other countries.** **We urge the NSC to start this review as soon as the outcome of the NICE appraisal and the potential of a Managed Access Agreement and the outcome of further deliberation about extending treatment in Scotland is known.** **We request that if other criteria are met, any current population uncertainties should not hold up the possibility of progressing a 5q SMA newborn screening programme.** **We note, that when used in newborn screening programmes in the USA, the information**

		about *SMN2* copy number and other tests are being considered as sufficient to predict the severity of an infant's 5q SMA and to establish which children should be treated and which monitored. **We ask that if testing is introduced in the UK it would need to be made clear to parents that the test is for 5q SMA, the most common form of SMA with clear information that this test does not cover all possible other very rare forms of SMA.** **We note that there is a growing body of clinical trial and real-world evidence of the effectiveness of nusinersen treatment for 5q SMA and that the earlier the treatment the greater the impact, with strong indications that the greatest impact occurs if it is started pre-symptomatically.** **We note that other treatments on the horizon are also indicating that the earliest possible treatment has the greatest impact.** **We note that there are significant ethical implications and dilemmas posed by newborn screening for 5q SMA. This is especially heightened with a treatment such as nusinersen, which is invasive in delivery (lumbar puncture) and requires further life-long treatment once every four months.** **We consider it vital that any screening programme is accompanied by a robust and ongoing programme of supportive counselling and accurate information about: what information may be revealed via the screening test; what impact the various types of 5q SMA have on life; what management and treatments are available.** **We note that evidence to date indicates a high level of support from the SMA community and the public for newborn screening for 5q SMA.** **Again, we note that at this stage it is not known which children will be able to access nusinersen treatment in the UK. This decision and the possible criteria for a proposed screening programme are critical to any further debate and decision making which, as**

		stated above, we consider to be imperative at this time.

Please return to the Evidence Team at screening.evidence@nhs.net **by 9th September 2018**

From Genetic Alliance UK

Name	Dr Jayne Spink	**Email address:**	XXXX XXXX
Role:	Chief Executive		
Organisation (if appropriate):	Genetic Alliance UK is the national charity working to improve the lives of patients and families affected by all types of genetic conditions. We are an alliance of over 180 patient organisations. Our aim is to ensure that high quality services, information and support are provided to all who need them. We actively support research and innovation across the field of genetic medicine. Rare Disease UK is a multi-stakeholder campaign run by Genetic Alliance UK, working towards the delivery and implementation of a national strategy for rare diseases in the UK. The UK Strategy for Rare Diseases was published in November 2013. Pertinent to this consultation, the Strategy includes a commitment from all four Governments of the UK to: "Continue to work with the UK National Screening Committee to ensure that the potential role of screening in achieving earlier diagnosis is appropriately considered in the assessment of all potential new national screening programmes and proposed extensions to existing programmes." Commitment 9, The UK Strategy for Rare Diseases, November 2013. This commitment recognises the value that the rare disease community places on early diagnosis, not only for the benefits it can bring to an affected individual but because of the impact it can have on improving the quality of life for their whole family.		

Do you consent to your name being published on the UK NSC website alongside your response?

Yes X☐ yes **No** ☐

Section and / or page number	Text or issue to which comments relate	Comment *Please use a new row for each comment and add extra rows as required.*
p6	'The current review aims to synthesise and appraise the available evidence published	Given the breadth of the stated aims of the review, we question the decision to not to broaden the scope of the review to include the question as to whether a screening programme might be recommended for SMA caused by mutation of the SMN1 gene on

	since August 2012 concerning the viability, effectiveness and appropriateness of any of the screening pathways for SMA in a UK population.'	chromosome 5q (5q SMA) with infantile or childhood onset. This was recently added to the Recommended Uniform Screening Panel in the US. In addition to accounting for approximately 95% of cases, this group has a highly specific screening test, is better understood epidemiologically (including regarding the predictability of severity) and is the population for which a disease-modifying treatment (nusinersen) has been licensed. SMA represents a complex and variable set of conditions. Some of these are more severe and progress more rapidly than others. As stratified medicine becomes a reality and as genomic medicine begins to become mainstream in the UK, there are benefits to be gained from considering subtypes of conditions with identified genotypes as distinct conditions. We ask the UK NSC to consider whether targeted screening for clearly defined subgroups of the broader SMA condition group may meet criteria for recommendation, rather than delaying this important public health programme until a broader programme (referred to in the review as 'gold standard') is possible.
p9	'This review was limited to peer-reviewed literature published in English since August 2012 that was freely available.'	Relying solely on peer reviewed literature excludes the direct contribution of the patient voice to the process. While information from clinicians and patients may not be published, it represents the most recent and relevant information on a condition coming from those that either directly manage or are affected by the condition today. NHS England, the National Institute for Health and Care Excellence and the European Medicines Agency all have facility to consider evidence from patients and clinicians that is not sourced from peer reviewed literature. These agencies have accepted that evidence will always be scarce in the area of rare disease, and is likely to be of weaker statistical significance than that expected from more common conditions. They have resolved to fill this gap by accepting qualitative evidence from the patient community. We believe the UK NSC should take steps to do the same.
p9	'The previous UK NSC review did not investigate newborn screening, so studies on newborn screening published prior to August 2012 have	We do not follow the logic of this exclusion. Highly relevant material may be permanently excluded from the UK NSC's consideration.

	not been considered.'	
p16-17	'It is important to consider though, that diagnosis at this stage cannot determine how the disease will clinically manifest; the same number of copies of SMN2 may translate to disease of differing severity (that is, different types) in different patients, limiting the predictive power of antenatal analysis. This is important when considering the implications of antenatal screening as decisions concerning termination of pregnancy may rest on the potentially ambiguous results of a molecular test.'	It appears that antenatal screening is being held to a higher standard of predictability than many conditions already screened for. For a number of conditions that already form part of the Fetal Anomaly Screening Programme, such as Down syndrome, exomphalos and spina bifida, it is very difficult to predict how severely the fetus is affected until after the baby is born. In these cases, while it is possible to know approximately how the disease will clinically manifest based on information available during pregnancy, decisions about termination of pregnancy are having to be made based on imperfect information. It is not clear why the uncertainty in this case is different from the uncertainty in the cases listed above.

Please return to the Evidence Team at screening.evidence@nhs.net **by 9th September 2018**

NSC UK National Screening Committee

From Biogen Idec Ltd.

Biogen

Dear National Screening Committee,

In accompaniment to this letter, please find Biogen's response to the consultation on newborn screening in 5q spinal muscular atrophy (SMA). To aid review of our consultation response, a reference pack has been included in the accompanying email.

We are pleased that the NSC are committed to robustly reviewing evidence in areas such as SMA to determine the appropriateness of screening programmes. We hope that our response to this consultation will aid this process and complement the already existing evidence base.

Despite being a rare disease, SMA is the leading genetic cause of infant deaths. SMA is a single gene locus disorder. Patients with SMA are deficient in SMN protein, which causes progressive muscular degeneration and irreplaceable neuron loss. The longer the body is subjected to SMN protein deficiency the more irreplaceable neurons are lost. The sooner SMN protein levels can be increased, the better the outcome for the patient.

The single gene locus nature of the disorder lends itself to feasible high throughput Guthrie screening.

There is a growing body of evidence to support early intervention in trials of effective SMA drug therapies as well as multiple animal models. Biogen's clinical trials have shown how early treatment with nusinersen in the pre-symptomatic SMA population, greatly benefits patients as it delays or even prevents the onset of symptomatic SMA and allows children to develop with significantly less disability.

SMA science is progressing very quickly at present. The introduction of multiple effective disease-modifying therapies as well as advances in detection methods such as RT-PCR and validation using MLPA, suggests that an SMA screening intervention will be an inevitable conclusion. The recommendation by the RUSP in the US for a screening programme recognises the feasibility of conducting an effective screening programme.

A newborn screening programme for SMA and early intervention would greatly benefit those who suffer this disorder, allowing them to be treated before irreparable damage occurs which has life-threatening or life-long consequences. We concede that to surpass a high burden of evidence to support screening further research is required. Examining the research at congresses on this topic it is clear the availability of evidence is developing quickly worldwide. We ask that you consider what you can do as a committee to shorten the delay to implementing this life saving screening.

Yours sincerely,

XXXX XXXX

Biogen Idec Limited

XXXX XXXX

Name	Ben Tichler	**Email address:**	XXXX XXXX
Role:	**Senior Medical Manager SMA**		
Organisation (if appropriate):	Biogen Idec Ltd. Please note this consultation response was compiled under Biogen's guidance by Wickenstones Ltd.		

Do you consent to your name being published on the UK NSC website alongside your response?

Yes X☐ yes **No** ☐

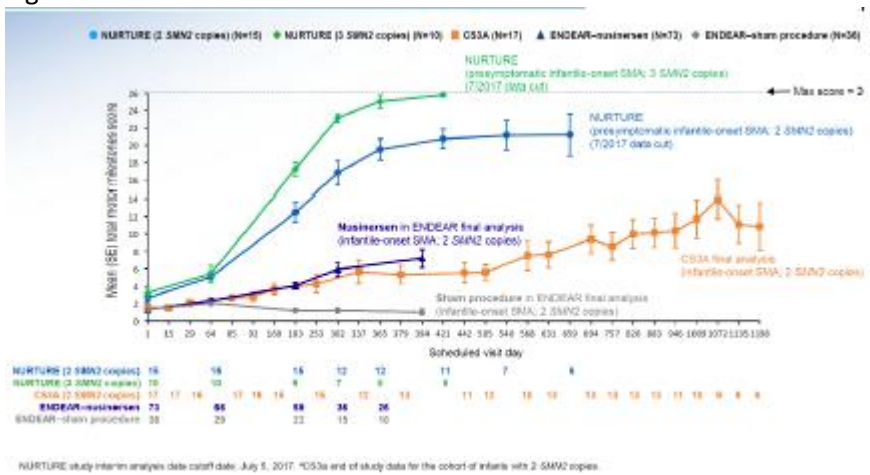
Section and / or page number	**Text or issue to which comments relate**	**Comment** *Please use a new row for each comment and add extra rows as required.*
Page 4	Plain English summary appears to a lay reader to communicate that SMA is not that severe overall due to only describing type 0 and type 4 instead of defining all types	Biogen would like to suggest improving the plain English summary to fully explain the severity of the condition by aligning it with the descriptions in the patient group submissions for the National Institute for Health and Care Excellence (NICE) and the Scottish Medicines Consortium (SMC). Despite being a rare disease, 5q spinal muscular atrophy (SMA) is the leading genetic cause of infant deaths.(1) Individuals with SMA are unable to make the SMN protein, which causes their muscles to gradually get weaker. As a result, patients lose the ability to move over time and eventually need help to breathe.(2,3) SMA can be grouped into 5 main types (type 0 to 4), based on the age that symptoms first appear and the level of movement abilities achieved before the patients starts to lose those abilities:(4) • Type 0 SMA, the most severe, affects babies before birth. Babies with type 0 SMA struggle to breathe at birth and often survive for only a few weeks after birth. • Babies with SMA type 1 develop severe muscle weakness which affects movement,

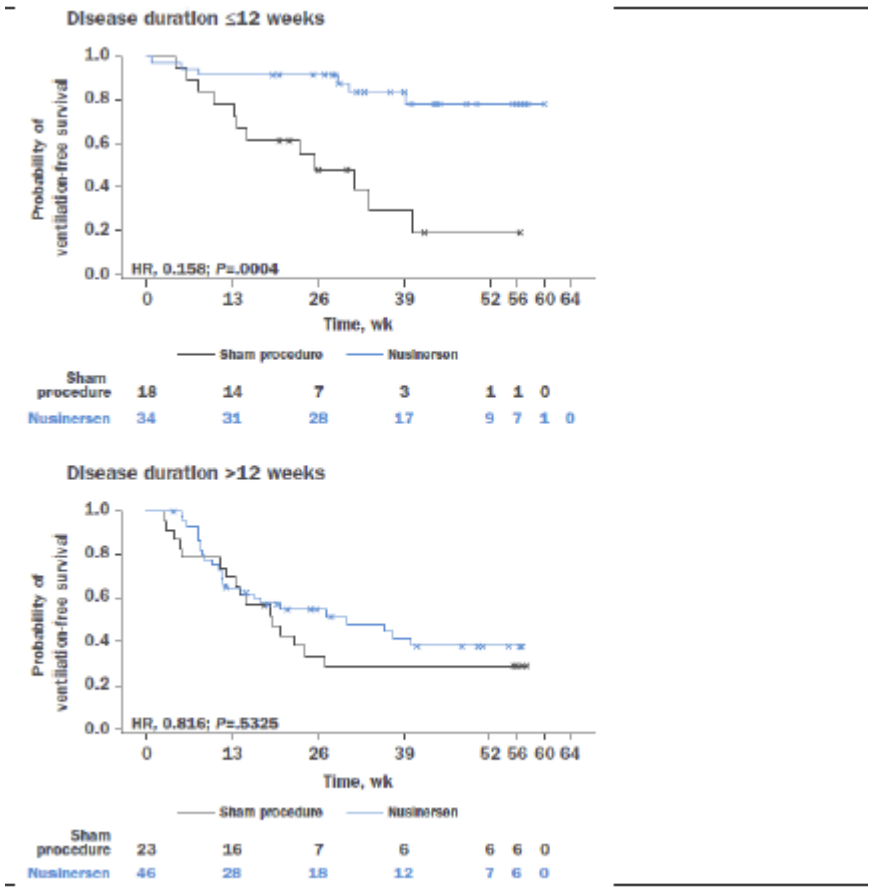
		swallowing and breathing before they are 6 months old. Babies with type 1 are never able to sit without help and without treatment are unlikely to survive their second birthday. • Children with type 2 SMA develop symptoms between 6 and 18 months of age. They are often severely disabled and unable to walk without help. • Children with type 3 SMA have different levels of muscle weakness that appear between 18 months and 18 years of age; most people with type 3 SMA can walk or sit without help at some point, but many lose this ability over time. • Type 4 SMA is the least severe and usually only affects adults. Adults with type 4 SMA live as long as adults without SMA and may just have mild muscle weakness. The above classification system is useful but does not always reflect the full extent of the disease. Regardless of subtype, the disease impacts significantly on the child/young person/adult's health and well-being, ability to live independently and inclusion in society.(5) Furthermore, managing SMA is physically, emotionally and practically demanding for both the person with the condition and their unpaid carer(s).(6)
Page 4	"This review identified evidence on a new treatment for SMA, called nusinersen. Studies have shown that nusinersen can improve symptoms in children with SMA. However, this evidence review did not find information on the effectiveness of nusinersen in children without symptoms, and there is no evidence on the long term effects of this drug."	There is substantial evidence on effectiveness of nusinersen in pre-symptomatic SMA patients: - Early treatment of the pre-symptomatic infant potentially prevents the onset of the SMA phenotype and allows for progressive gains in motor function and performance in the developing child. - As noted by Glascock et al (2018) and Govoni et al (2017), preclinical studies in mouse models of SMA consistently show the best results occur when treatment is given before significant motor weakness or loss is present.(7,8) - The latest interim analysis (5th July 2017) of the ongoing NURTURE study found that pre-symptomatic infants treated with nusinersen achieved motor milestones beyond those achieved by their sibling with SMA.(9) These results are inconsistent with the natural history of sibling pairs with SMA in which most siblings (86.6%) have concordant phenotypes.(10) Furthermore, every infant continues to make progress throughout the duration of the study without sustained evidence of regression.(9) There is evidence on the long-term effectiveness of nusinersen in SMA for infantile (type

		1) and later onset (type 2/3) patients: - Longer-term data are available from the phase II study CS3A (3.3 years), and the phase I study CS2 and its extension CS12 (2.9 years). These data support the maintenance of effect with long-term treatment (including beyond the age of 24 months).(11,12) - Interim results (30th June 2017) are also now available from the long-term extension study, SHINE, for 89 patients. Participants who either continued on nusinersen from the ENDEAR study or who transitioned to nusinersen after receiving the sham-control, experienced improved motor function and improved event-free survival time. The median time to death or permanent ventilation in the group who received nusinersen in ENDEAR and continued in SHINE was 73.0 weeks, significantly longer than 22.6 weeks for those who received sham-control in ENDEAR. The analysis also confirmed observations from other studies that the benefits are greatest with early treatment.(13–16) - In addition, there has been no evidence of lessening of effect over time. This was confirmed by an expert panel who suggested that the mechanism of action was a strong reason to believe that the effects seen in the clinical studies can be extrapolated over time, and may in fact continue to improve.
Page 5	"In the UK, there are currently no approved, disease-modifying treatments for SMA and current management involves a holistic approach to disease symptoms."	Biogen would like to request the amendment of this sentence. An approved disease-modifying treatment has been available for SMA in the UK ever since nusinersen was authorised for marketing throughout the EU by the European Medicines Agency (EMA) (17) on 30th of May, 2017. In addition, Biogen would like to suggest adding the SMC's approval of reimbursement of nusinersen for type 1 patients in Scotland, please see: https://www.scottishmedicines.org.uk/medicines-advice/nusinersen-spinraza-fullsubmission-131818/.
Page 6	"All current approaches to screening are limited in their ability to predict the type of SMA that an individual will develop and the severity of the disease. Whilst studies have shown that a higher	SMN2 is a key determinant of disease phenotype and is routinely determined after initial diagnosis to help predict the clinical phenotype. All patients possess a low-functioning analogue to the SMN1 gene called SMN2. Humans have a variable copy number of the SMN2 gene (0-8 copies), which correlates with the amount of SMN protein that is produced. SMN2-derived SMN protein can compensate for the SMN1 deletion to a limited degree, therefore the SMN2 copy number is predictive of clinical severity. Importantly, in the context of newborn screening, genetic testing of 375 patients with

	SMN2 copy number correlates with a milder clinical phenotype, it is not currently possible to accurately predict phenotype severity. It is important that tests are accurate so that individuals can make informed decisions about their pregnancies or treatments."	SMA types 1-3 demonstrated that 80% of patients with SMA type 1 carry 1-2 SMN2 copies, and 82% of patients with SMA type 2 carry 3 SMN2 copies, whereas 96% of patients with type 3 SMA carry 3-4 SMN2 copies(18) Thus, it is highly likely an infant identified by newborn screening with subsequent testing showing 2 or fewer copies of SMN2 will be severe in phenotype. Glascock et al (2018) report how although there is not a perfect correlation between SMN2 copy number and SMA type, the correlation is strong enough to make a suitable treatment algorithm for pre-symptomatically diagnosed SMA.(7) All the above considered, we would like to draw the attention of the NSC to a potential biomarker for disease activity to guide therapy in the presymptomatic population. Darras et al (2018)(25) investigated whether phosphorylated neurofilament heavy chain (pNF-H) could function as a potential biomarker. Phosphorylated neurofilament has been demonstrated as a marker for neuron axonal damage. Darras examined the association between pNF-H and age, SMA symptom severity and SMN2 copy number. They observed higher mean plasma pNF-H levels in children with SMA than non-SMA children and concluded that patients with fewer SMN2 copies generally have higher pNF-H plasma levels. The highest pNF-H levels were observed in pre-symptomatic infants with 2 copies of SMN2, suggesting that SMA-associated neurodegeneration may be identifiable shortly after birth and prior to patients becoming symptomatic. When patients were treated with nusinersen, rapid decline and then stabilisation to normal levels of plasms pNF-H was observed. The authors concluded that pNF-H levels could be a useful biomarker but mention that further validation and research is required. We would like to suggest that this is an area of potential research for the NSC.
Page 7-10	Summary of recommendations	We would like to suggest updating the summary of recommendations to reflect the comments and corrections made in this document.
Page 14	The text mentions that NICE is conducting an STA for nusinersen	Please also add the approval of reimbursement of nusinersen for type 1 patients in Scotland (see: https://www.scottishmedicines.org.uk/medicines-advice/nusinersen-spinraza-fullsubmission-131818/) and that other types of SMA may be considered on a type by type basis on individual funding requests.
Page 14	"However, recent trials (for example, NURTURE [ClinicalTrials.gov registration NCT02386553]; ENDEAR	Please note that only NURTURE included pre-symptomatic patients. An analysis conducted on subgroups within both the ENDEAR and CHERISH randomised controlled trials (RCTs) revealed that greater efficacy is achieved with earlier treatment, however ENDEAR and CHERISH excluded pre-symptomatic patients

	[NCT02193074]) are now focusing on treating infants with genetically diagnosed, pre-symptomatic SMA to prevent degeneration before it begins"	from its trial and focussed on the symptomatic type 1-3 population. NURTURE treated SMA patients before symptom onset and showed that nusinersen is effectively targeting the underlying disease pathophysiology and preventing irreversible motor neuron damage.(11,15,16,26)
Page 14	"Interim results from the Phase II NURTURE study assessing the efficacy and safety of nusinersen in infants with pre-symptomatic SMA have shown there were improvements in mean Hammersmith Infant Neurological Examination (HINE) motor milestones scores verses baseline, although the study did not compare pre-symptomatic treatment to treatment after symptoms start."	Biogen would like to suggest rewording or removing the statement that the study did not compare pre-symptomatic treatment to treatment after symptoms start, to avoid suggestion that the trial was not designed appropriately. As the NURTURE study was a single-arm study it was not possible to compare pre-symptomatic treatment to treatment after symptoms start, however to address this, a comparison of patients treated both pre-symptomatically and after symptom onset was made across studies, as explained below and illustrated in Figure 1 below. NURTURE is a phase II, open-label, multicentre, multinational, single-arm study to assess the efficacy, safety, tolerability, and pharmacokinetics of multiple doses of nusinersen in subjects with genetically diagnosed and pre-symptomatic SMA. Treated subjects enrolled in NURTURE were compared to their untreated siblings (from whom data was collected separately from the NURTURE study) in terms of achieving age-appropriate motor milestones of sitting and walking. The natural history of SMA suggests that most siblings with SMA (86.6%) have concordant phenotypes (i.e. the presence of the same symptoms/severity of disease).(10) The comparison across studies (Figure 1) shows that the greatest improvements in total HINE-2 motor milestones were observed in infants treated with nusinersen in the pre-symptomatic stage of SMA in NURTURE. In a real word setting the pre-symptomatic patients enrolled in the NURTURE trial would be identified by newborn screening. The benefit of earlier treatment is further illustrated in ENDEAR (phase III study in patients with infantile onset [type 1] SMA), in which event-free survival time in nusinersen-treated patients with ≤12 weeks disease duration was longer than in nusinersen-treated patients with >12 weeks disease duration (Figure 2).

		Overall, the above mentioned observations, as well as subgroup analyses of the CHERISH trial and the extension trial SHINE, suggest patients have greater benefits with earlier treatment.(13–16) For clarity patients in ENDEAR and NURTURE have the same dosing regime, but vary by the time of onset of therapy. In Figure 1, patients in the blue NURTURE line and blue ENDEAR line both have only 2 copies of the phenotype modifier SMN2 gene. Figure 1: HINE-2 motor milestone scores across studies:  NURTURE study interim analysis data cut-off date: July 5, 2017. aCS3a end of study data for the cohort of infants with 2 SMN2 copies. Abbreviations: HINE-2, Module 2 of the Hammersmith Infant Neurological Examination; SE, standard error, SMA, spinal muscular atrophy; SMN, survival motor neuron NURTURE study interim analysis data cut-off date: July 5, 2017. aCS3a end of study data for the cohort of infants with 2 SMN2 copies. Please note all patients in the figure have 2 copies of SMN2 except the green nurture line. This is for clarity of comparison Source: DeVivo 2018(11) Figure: Event-free survival by disease duration in ENDEAR



Abbreviations: HR = hazard ratio
Source: Servais et al 2017(15)

The value of newborn screening was recognised by Glascock et al (2018) and Govoni et al (2017)(8), who reported that the diagnostic delay associated with symptomatic identification of SMA means that patients have progressed past the point where maximal benefit is achievable before therapeutic interventions occur.(7) Govoni et al (2017)(8)

		adds that the timing of an intervention matters. Most of the degeneration in motor neurons takes place during the first few months of life in SMA type 1 patients. Furthermore, the NURTURE trial, subgroup analyses of ENDEAR and CHERISH, and the extension trial SHINE, suggest patients have greater benefits with earlier treatment.(14–16,26)
Page 15	Newborn screening	On page 15, it is announced that each of the screening approaches will be summarised further below, however, antenatal screening and newborn screening are summarised under one heading, which is confusing and conflates some of the risk-benefit analysis. For further comments, see below.
Page 16	"It is important to consider though, that diagnosis at this stage cannot determine how the disease will clinically manifest; the same number of copies of SMN2 may translate to disease of differing severity (that is, different types) in different patients"	In several instances in the document, mention is made of the absence of a correlation between SMN2 copy number and disease severity. However, we feel this may not be a barrier to screening as pointed out before in our response to the same issue on page 6 of the review and of which the supporting evidence is reiterated below. Glascock et al (2018) report how although there is not a perfect correlation between SMN2 copy number and SMA type, the correlation is strong enough to make a suitable treatment algorithm for pre-symptomatically diagnosed SMA.(7) This is further backed up by Prior 2010,(19) conducting a review into available evidence on SMA. Prior 2010 writes on the association between genotype and phenotype and describes the studies by Campbell et al (1997), McAndrew et al (1997), Wirth et al (1999) and Mailman et al (2002),(20–23) which have shown that SMN2 copy number modifies the severity of the disease. The conclusions of the above are illustrated in the genetic testing of 375 patients with SMA types 1-3 and demonstrating that 80% of patients with SMA type 1 carry 1-2 SMN2 copies, and 82% of patients with SMA type 2 carry 3 SMN2 copies, whereas 96% of patients with type 3 SMA carry 3-4 SMN2 copies(18) Thus, it is highly likely an infant identified by newborn screening with subsequent testing showing 2 or fewer copies of SMN2 will be severe in phenotype.
Page 17	"Various ethical implications could result from the introduction of a screening programme, whether this is	It is unclear how much of the comments relate to newborn screening. The survey on newborn screening is mentioned alongside antenatal screening with no clear differentiation between the two. The identification of newborns with SMA does not carry the same ethical implications as

	carrier screening, antenatal screening or newborn screening; therefore, population-based pilot studies have been conducted investigating these social issues. One survey showed overwhelming support from expectant couples for newborn DBS screening for SMA, even considering a lack of treatment development. However, another survey of families affected by SMA found that although 75% of families were in favour of screening in some form, they had concerns including carrier stigmatisation, social engineering and, for antenatal screening in particular, the risk of termination when a high quality of life could still potentially be achieved. Therefore, if screening were to be implemented, the provision of genetic counselling should be carefully timed and given appropriately."	carrier or antenatal screening. Newborn screening helps to determine the need for treatment before symptoms of disease inevitable appear; this allows patients and families the chance to initiate treatment earlier. Postnatally there is no option to terminate life. Thus comments on "social engineering" are not relevant here. Boardman et al. mention that there are 2 concerns with newborn screening: concerns about the impact of newborn screening on the early experiences of the family and the inability to treat due to lack of efficacious treatments.(27) With the licencing of nusinersen in presymtomatic children as well as the advent of other therapies we feel the lack of efficacious therapy may be less of a concern for families. Biogen would like to suggest that this paragraph splits out antenatal and newborn screening such that the risks and benefits are clear.
Page 18	"However, one implication could be the risk of a false	According to Chiang 2017(28) and Staropoli 2017 (29), it is possible to reduce false positives using a 2nd tier test. Results of further screening tests are reported below:

	positive test and the impact this may have on families and the initiation of any unnecessary treatment."	A screening trial of 120,267 newborns at the National Taiwan University Hospital used a combination of a real-time polymerase chain reaction (RT-PCR) and a second-tier droplet digital PCR (ddPCR) to accurately diagnose SMA from dried blood spot (DBS) samples with no false positives. (24) The procedure entailed newborn DBS acquired via a heel stick. The eight false positives detected with RT-PCR were all excluded using the second-tier ddPCR assay. A pilot screening trial of 3,826 newborns at 3 hospitals in New York state between January 2016 and January 2017 tested for homozygous and heterozygous SMN1 exon 7 deletions.(30) The screen was successful in identifying one neonate with SMA. No false negatives or false positives were identified during the course of the pilot study. Invasiveness of the method was minimal, with results obtained from routine newborn DBS acquired via heel stick. Improved primers and labels for the RT-PCR as used in the New York state protocols prove SMA newborn screening to be both feasible and with minimal risk of false positives, this is confirmed by MLPA. Of note are innovative RT-PCR methods recently developed to reliably detect SMN1 absence from the same DBS punch used to screen for severe combined immunodeficiency (SCID).(31) Moreover, Biogen note that in phenylketonuria (PKU) (part of the UK newborn blood spot [NBS] screening programme), there is a 90% risk of false positives, meaning that all newborns testing positive for PKU need another test.(32)
Page 20	"Secondly, a newborn diagnosed with SMA may be treated immediately after birth with invasive treatments such as nusinersen, which is administered via spinal injections, although without treatment they may only have developed a mild form of the disease that did not require treatment."	Biogen would like to request amending this sentence. None of type 0-3 SMA patients should be described as having a mild form of the disease, as they are all debilitating. According to the literature, the majority of SMA patients have type 1 (60%). These children are never able to sit unsupported and typically die within the first two years of life.(33,34). SMA type 2 accounts for approximately 27% of patients, children with significant disability. SMA type 3 accounts for approximately 12%.(33,34) Patients outside type 1-3 therefore account for less than 5% of patients. Although some patients with type 2 and most patients with type 3 SMA survive into adulthood, the considerable morbidity of the disease is associated with lifelong impacts on health-related quality of life, ability to live independently and requirements for care because of contractures to the lower extremities, hypermobile joints in the upper extremities and recurrent fractures.(5,35,36) Pain caused by severe contractures, osteoporosis, vertebral fractures, orthopaedic procedures or muscular overuse, is also a

		frequent occurrence and major feature of SMA.(37) Furthermore, type 2 and type 3 SMA imposes a major physical and psychological burden due to the progressive decline in health, including fear of losing independence, struggle with feeding and impaired breathing.(36–38) symptom severity and SMN2 copy number. They observed higher mean plasma pNF-H levels in children with SMA than non-SMA children and concluded that patients with fewer SMN2 copies generally have higher pNF-H plasma levels. The highest pNF-H levels were observed in pre-symptomatic infants with 2 copies of SMN2, suggesting that SMA-associated neurodegeneration may be identifiable shortly after birth and prior to patients becoming symptomatic. When patients were treated with nusinersen, rapid decline and then stabilisation to normal levels of plasms pNF-H was observed. The authors concluded that pNF-H levels could be a useful biomarker but mention that further validation and research is required. We would like to suggest that this is an area of potential research for the NSC. Only type 4 could be classed as a truly milder form of the disease but is rarely diagnosed and has low prevalence.(4) Moreover, Glascock (2018)(7) describes a treatment algorithm for SMA-positive infants, identified through newborn screening on SMN2 copy number, differentiating those with a high need (1-3 SMN2 copy number) vs. those who can watch-and-wait (≥4 SMN2 copy number including type 4 SMA). This would ensure infants could avoid invasive treatment too early in their life. Other biomarkers for disease activity could guide therapy in the presymptomatic population. Darras et al (2018)(25) investigated whether phosphorylated neurofilament heavy chain (pNF-H) could function as a potential biomarker. Phosphorylated neurofilament has been demonstrated as a marker for neuron axonal damage. Darras examined the association between pNF-H and age, SMA
Page 20	“Finally, since SMN1 is particularly prone to de novo mutations (that is, mutations that are acquired within a lifetime rather than being passed on from generation to generation), there is the risk of false negative results from	The reporting of false negative antenatal or newborn tests upon de novo SMN1 mutations is incorrect and Biogen request a revision of this statement. While de novo mutations are acquired during a lifetime, de novo mutations occuring in a parent’s gametes may be passed on to the next generation (in contrast to what is incorrectly stated in the consultation document and incorrectly referenced to the Prior 2008 article [reference 13 in the consultation document]). De novo germline mutations are relevant for carrier screening, whose purpose would be to identify couples at risk for having a child with SMA. De novo mutations in SMN1 have been found to occur in 2% of

	antenatal or newborn tests."	patients(39), which in the majority of cases, are due to paternal meiosis, i.e. inherited from the father. This means that in 2% of patients, carrier screening would have identified a father of a de novo SMN1 patient as a false negative. Nevertheless, an antenatal or newborn screen would have identified the patients (i.e. the children of fathers carrying the de novo SMN1 mutation in his germline) as positive for the SMN1 mutation. Patients with a false negative result at antenatal or newborn test would still be diagnosed on symptomatic presentation, so would be at no greater disadvantage than without the newborn screening. The 2% of SMA cases that are affected by this does not warrant the 'particularly prone' label. Moreover, due to the extremely debilitating nature of the disease as described before, false negatives should not be a reason to prevent the introduction of a newborn screening programme that could transform the nature of the disease through early treatment. Furthermore, patients with a false negative result would still be diagnosed on symptomatic presentation, so would be at no greater disadvantage than without the newborn screening.
Page 24-31	Accepted evidence. The following is being excluded: • Individuals who do not live in the UK • Retrospective or case control studies • Narrative reviews, commentaries or letters • Conference abstracts or other publication types that have not been peer-reviewed • Retrospective studies	Biogen would like to point out that the accepted evidence and exclusion criteria mentioned by the NSC are much more limiting than of other evidence review bodies across the world, including the US Food and Drug Administration (FDA), the EMA, the SMC and NICE. For instance, when conducting a NICE systematic literature review, the studies excluded in the current review would still be taken into consideration. NICE follow the Centre for Reviews and Dissemination's (CRD's) guidance for undertaking reviews in healthcare, which states the importance of including conference abstracts and ongoing/unpublished studies (where available), and also notes that if the inclusion criteria are too narrowly defined there is a risk of missing potentially relevant studies and the generalisability of the results may be reduced. This is particularly relevant for an orphan disease where data may be limited due to the small patient population and research may be conducted over a broader geographical area.(40)
Page 35	"Moreover, the study only considered SMA caused by SMN1 mutations, and did not	This statement suggests that this would be a significant problem. However, regardless of clinical severity, 95% of all SMA patients have the same homozygous SMN1 gene deletion, and detection of the SMN1 gene deletion is used as the primary diagnostic assay.(18)

	look at other cause of SMA other than SMN-related mutations. Therefore, these remaining patients will not have been captured in the incidence calculations, which may lead to an underestimation of the true incidence of SMA. These limitations make it difficult to assess the extent to which the evidence is applicable to the general UK population."	Furthermore, SMA due to mutations in SMN1 is the only form of SMA for which there are currently disease modifying treatments available and in late stage development. Moreover, due to the extremely debilitating nature of the disease as described before, patients should not be disadvantaged by delaying the introduction of a newborn screening programme that screens for SMA which could transform the nature of the disease through early treatment. Furthermore, patients with a false negative result would still be diagnosed on symptomatic presentation, so would be at no greater disadvantage than without the newborn screening
Page 35	"This study reported an incidence of 10.9 cases per 100,000 live births, which is not consistent with the incidence of 1 in 24,119 births (calculated as 4.15 per 100,000 births) reported by the study from north-east England identified in the previous UK NSC review. Although the current study is larger, the unclear methodology means that it is uncertain whether this finding is a more accurate estimation of the incidence of SMA in the UK. Overall, there are substantial limitations in the evidence base for this question, and	SMA is an orphan condition and is therefore subject to the same limitations as other orphan conditions when estimating true incidence and prevalence of the condition. The Committee for Orphan Medicinal Products at the EMA (COMP) recognises the difficulties in obtaining relevant morbidity data to demonstrate prevalence in very rare diseases or conditions.(41) In their recommendations, they state the estimated prevalence of the condition at a certain point in time is acceptable as long as there is reasonable evidence that the estimate provided is a good approximation of the true prevalence of the condition in the EU at the time of application. Similar observations are made for incidence data. The COMP granted orphan designation to nusinersen in 2012 based on a prevalence rate of 0.4 per 10,000 people (equivalent to 4 per 100,000); incidence data were not discussed.(42) However, due to the severity of patients with subtypes 1–3, the few patients affected and the need for referral to a specialist paediatrician, underestimation of the incidence of SMA is extremely unlikely. As highlighted in Glascock (2018)(7), type 4 patients would not need immediate treatment, but rather be monitored until intervention is required (which may or may not happen). As addressed before, Biogen disagree with the conclusion on inability to determine the individual's prognosis from their genotype (please refer to our responses raised to pages 6 and 16 of the review).

	there was no further evidence identified to indicate that it is possible to determine an individual's prognosis from their genotype. Therefore, this criterion is not met."	
Page 36	"However, a number of limitations to this method were discussed. These included a risk of false negative test results because: • SMA carriers that have two or more SMN1 copies located on a single chromosome would not be detected. This was a particular concern in the African-American population in the US, but it is unclear if any subgroups of the UK population would be similarly affected • SMN1 de novo mutations, which occur in approximately 2% of SMA patients (1% of parents) would not be detected • 3% to 4% percent of patients, i.e. 1% to 2% of carriers have small intragenic mutations in the SMN1 gene and when paired with SMN1 deletion, this genotype	False negatives are a risk with screening for any condition that is not apparent until symptoms develop e.g. phenylketonuria (PKU). The statement suggests that false negatives would be a significant problem. However, regardless of clinical severity, 95% of all SMA patients have the same homozygous SMN1 gene deletion, and detection of the SMN1 gene deletion is used as the primary diagnostic assay.(18) Therefore, false negatives only affect approximately 5% of patients and due to the devastating nature of the disease should not be a barrier to screening.

	cannot also be identified by quantitative analysis of SMN gene copies"	
		As a comparison, estimates of false negatives range from 1.7–5.4% of children in Cystic Fibrosis Newborn Screening in part due to the delta F508 genotypic distribution of the population tested. Furthermore, screening does not delay the identification of cystic fibrosis in children with a negative result.(43) Furthermore, false negatives do not put SMA patients at any further disadvantage than without any screening programme in place as they would still be diagnosed when symptoms start to appear. If a specific population is known to be at a higher risk of a false negative, they can be tested using a 2nd tier assay. This approach was tested successfully in a Taiwanese screening trial, where a hybrid allele of SMN1 present in the Taiwanese population gave rise to a false positive results which were subsequently invalidated with ddPCR and MLPA.(24)
Page 44	"The majority of index tests used in the included studies to screen for SMA in neonates only identified SMN1 exon 7 deletions, and as this is not the only known underlying cause of SMA, these tests do not represent a comprehensive screening test for all known causes of the condition."	As mentioned before, the SMN1 exon 7 deletion accounts for 95% of all SMA cases. Although the test would not cover 100% of all SMA cases, it would represent very meaningful progress in this debilitating disease. Furthermore, a screening trial was carried out successfully (100% positive prediction value using RT-PCR and MLPA assay) between November 2014 and September 2016 in which 120,267 newborns were screened to detect homozygous deletions in the SMN1 intron 7.(24)
Page 45	"There is evidence from two studies that mCOP-PCR and HRM analysis are highly sensitive and specific newborn SMA screening methods; however, in the	As mentioned before, the SMN1 exon 7 deletion accounts for 95% of all SMA cases. Although the test would not cover 100% of all SMA cases, it would represent very meaningful progress in this debilitating disease. Biogen would like to draw attention to the following information to support the rationale

	absence of high-quality prospective screening studies using these methods in the general population, it is not possible to confirm these results. These methods identify SMN1 exon 7 deletion, which limits the applicability of the methods to the review question because this is not the only underlying cause of SMA, and as a result will not identify all SMA cases. Furthermore, there are also high risk of bias and applicability concerns since many of the studies identified were not evaluating screening studies in a randomly recruited and potentially unrepresentative population.“	for an SMA screening programme despite what the review describes as an absence of studies. Due to SMA being an orphan disease as noted by both the FDA and EMA(42,44) evidence generation in this area is naturally more limited. However, Biogen do not believe that should be reason to exclude studies in this area. Evidence review bodies across the world recognise this and are willing to accept evidence at the expected standard for orphan drugs. Biogen would like to request that the NSC review reviews evidence on the same bases as bodies such as the FDA, EMA, NICE and SMC. Moreover, the US Recommended Uniform Screening Panel (RUSP) issued a recommendation for newborn screening on the 8th of February, 2018.(45) Biogen believe that this is a great step forward and hope that the NSC will be able to make a similar consideration in the not too distant future. Additional studies on newborn screening in SMA include Chien 2017,(24) which demonstrates the feasibility of newborn screening using the RT-PCR assay. Of the 120 267 newborns, 15 tested positive according to the RT-PCR assay. A second-tier ddPCR assay excluded 8 false positives, and the other 7 patients were confirmed by the MLPA assay. Inclusion of the second-tier DBS ddPCR screening assay resulted in a positive prediction value of 100%.(24) Kraszewski 2017(30) reports results of a pilot based in New York state. The authors validated a multiplex TaqMan RT-PCR assay using DBS for SMA. They screened 3,826 newborns and tested for SMN1 exon 7 deletion. They identified one newborn with a homozygous SMN1 deletion and two copies of SMN2 linked to type 1 SMA. The pilot demonstrated the feasibility of population-based screening, acceptance by families and the benefit of newborn screening for SMA. The authors recommended that SMA would be considered for addition to the national RUSP. Biogen ask the NSC to consider implementing a pilot to provide the required evidence to implement a nation-wide screening programme
Page 49-51	Presentation of evidence on nusinersen	The review has highlighted two studies on nusinersen: Finkel 2017 and Mercuri 2018. Biogen would like to note that there are far more published studies available on the efficacy and safety of nusinersen, including long-term data. The European public assessment report (26) as published by the EMA gives a comprehensive overview of the nusinersen clinical trial programme. Currently, the Costello Medical review does not include data from CS3A (Finkel 2016)(46) CS2 and CS12 (Chiriboga 2017)(12) and in

		addition, the long-term extension SHINE, as published by Castro (2018)(13). The review also mentions the premature termination of the RCTs. Biogen would like to highlight that this was stopped on the request of an external impartial ethics board following positive statistical analysis of the primary endpoint at the interim analysis due to a statistically significantly improvement in the primary endpoint.
Page 53	"There are limitations to the evidence on nusinersen: there were only two studies on this treatment in trials with a small number of different participants making it difficult to draw conclusions; each study had a small number of participants; and there are no studies reporting the long term efficacy or safety of nusinersen."	The FDA, EMA, SMC, NICE and clinical experts all concluded that there is statistically significant value in nusinersen. Biogen would like to request an update to this statement, as for an orphan disease (and therefore by definition patient numbers are limited) having two RCTs is a major achievement. Biogen's RCTs are of high quality which was stated on page 51, accepted by the review on page 58 and clinical trial results were accepted by the bodies as just quoted. The RCTs met their primary endpoint (early), and therefore conclusions can be drawn as per the trial design and statistical analysis plan.(26,44,47). Finally, in the UK, the SMC has accepted nusinersen for reimbursement in type 1 SMA. The summary of the review can be quoted as saying: "In randomised, controlled, phase III studies of children with SMA, nusinersen treatment was associated with significant improvements in motor function compared with a sham injection. In infants with type 1 SMA, nusinersen significantly prolonged the time to permanent assisted ventilation or death." (47) Interim results (30th June 2017) are also now available from the long-term extension study, SHINE, for 89 patients. Participants who either continued on nusinersen from the ENDEAR study or who transitioned to nusinersen after receiving the sham-control, experienced improved motor function and improved event-free survival time. The median time to death or permanent ventilation in the group who received nusinersen in ENDEAR and continued in SHINE was 73.0 weeks, significantly longer than 22.6 weeks for those who received sham-control in ENDEAR. The analysis also showed the benefits are greatest with early treatment.(13)
Page 57	"This updated analysis of the evidence for a population-wide carrier screening programme for SMA against the UK NSC criteria did not identify sufficient evidence to	Biogen would like to request that the NSC re-consider their conclusion based on the evidence as presented in this document. We feel the instigation of SMA screening is more a question of when rather than if. In the coming years, many more treatments for SMA will be coming to market (see below). Because it takes considerable time to implement a national screening programme, Biogen would like to request the NSC consider making recommendations for further research into the feasibility or acceptability of newborn

	support a change in the previous recommendation."	screening in the UK. In the next years, the availability of evidence will increase and by preparing now, there will be a shorter delay to implement screening that could save lives. Future therapies in SMA There are five additional therapies in development for the treatment of SMA, including SMN1 gene replacement therapy, small molecules designed to alter SMN2 mRNA splicing, and additional small molecule approaches aimed at motor neuron protection and muscle enhancement. AVXS-101, a gene therapy to replace the SMN1 gene, is sponsored by AveXis (clinical trial identifier: NCT02122952). LMI070, a small molecule designed to alter splicing of SMN2 mRNA and increase the amount of functional SMN protein, is sponsored by Novartis Pharmaceutical (clinical trial identifier: NCT02268552). RO7034067 and RO6885247, small molecules designed to alter splicing of SMN2 mRNA and increase functional SMN protein, are sponsored by F. Hoffmann – La Roche (clinical trial identifiers: NCT02633709, NCT02240355, NCT02908685, NCT02913482). Finally, CK-2127107, a small molecule to enhance muscle contraction, is sponsored by Cytokinetics (clinical trial identifier: NCT02644668).
Page 57	"The main reasons for this are poor-quality evidence on the epidemiology of SMA, including total prevalence and how many people are affected by each type of SMA, the accuracy of screening tests, the effectiveness of screening programmes in the UK population, and the optimal diagnostic and treatment pathway following a screening programme. Although UK-based surveys	As per the evidence presented in this document, Biogen would like to request that the NSC reconsider their conclusions. In particular the statement on poor-quality evidence as this does not concur with conclusions from the FDA, EMA, NICE and SMC. SMA is an orphan disease and therefore criteria for evidence cannot be the same as for more prevalent conditions. The availability of evidence (as mentioned in this document) on the benefits of pre-symptomatic treatment through the NURTURE clinical trial combined with the availability of pilot studies in Taiwan and New York and the approval of nationwide newborn screening in the US should provide a good starting point for the evidence base. With the introduction of nusinersen as a disease-modifying therapy, as well as the range of other treatments in development, patients now have feasible treatments available that can transform the course of their disease. The introduction of a screening programme in the UK could prevent irreparable damage to motor neurons in newborns affected by SMA and allow patients access to the best possible quality of life through early treatment with nusinersen. Due to nusinersen and other forthcoming therapies, Biogen strongly believe

	of the general public and families affected by SMA have found support for the idea of a newborn screening programme,48, 75 this review did not find any studies that implemented a population-based screening programme and reported uptake of the test."	in the benefits newborn screening could bring to patients and families and hope that the NSC would be willing to make recommendations for further research into an SMA screening programme in the UK. This request is supported by a wide body of evidence that extends further than the current review suggests, and includes: - The latest interim analysis (5th July 2017) of the ongoing NURTURE study, which found that pre-symptomatic infants treated with nusinersen achieved motor milestones beyond those achieved by their sibling with SMA. These results are inconsistent with the natural history of sibling pairs with SMA in which most siblings (86.6%) have concordant phenotypes. Furthermore, every infant continues to make progress throughout the duration of the study without sustained evidence of regression.(11) - Longer-term data are available from the phase II study CS3A (3.2 years), and the phase I study CS2 and its extension CS12 (2.9 years). These data support the maintenance of effect with long-term treatment (including beyond the age of 24 months).(11,12) - Interim results (30th June 2017) from the long-term extension study, SHINE, for 89 patients. Participants who either continued on nusinersen from the ENDEAR study or who transitioned to nusinersen after receiving the sham-control, experienced improved motor function and improved event-free survival time. The median time to death or permanent ventilation in the group who received nusinersen in ENDEAR and continued in SHINE was 73.0 weeks, significantly longer than 22.6 weeks for those who received sham-control in ENDEAR. The analysis also showed the benefits are greatest with early treatment.(13) - Successful screening trials in Taiwan and New York state(24,30) - Expert recommendations for newborn screening reported in Glascock et al (2018) including recognition of the opportunities for maximal therapeutic benefit for patients with SMA identified through newborn screening.(7)
Page 57	"This review update identified a single study reporting UK-specific data for the prevalence of SMA at birth; however, the study did	Many efforts have been made to capture the prevalence of SMA in the UK. However, because SMA is a rare condition, it is very difficult to conduct a large, prospective study of SMA epidemiology. Furthermore, the time taken to capture these data would significantly delay the introduction of a screening programme. Therefore, because it takes considerable time to implement a national screening programme, Biogen would like to

	not present data by SMA type within the UK population. Without large, prospective studies of SMA epidemiology in the UK population it is not possible to determine the possible impact of a population screening programme."	request the NSC consider intermediate steps such as instating a pilot programme, which would also help to capture these data and evaluate the possible impact of a population screening programme.
Page 57	"Similarly for newborn screening, tests were only able to identify SMN1 exon 7 deletions which is not the only underlying cause of SMA, therefore they were not sufficient to detect all SMA patients compared to a gold standard that was able to identify all patients. The true accuracy of carrier screening or neonatal screening cannot be confirmed without studies comparing the tests to gold standards in well-designed prospective studies."	As mentioned before, SMN1 exon 7 deletion captures 95% of patients which would represent significant progress for patients and families. Moreover, due to the extremely debilitating nature of the disease (as mentioned before) it is likely that SMA patients not identified through newborn screening would be diagnosed when symptoms present, meaning they are no worse off having undergone screening. Furthermore, there is no clarity in the report as to what is considered to be the gold standard. Other conditions with approved screening programmes in the UK, e.g. PKU and cystic fibrosis, are not able to identify all patients from testing and carry the risk of false positives and false negatives.(48,49)
Page 58	"However, the current review found promising results on nusinersen. Two high-quality RCTs reported better outcomes on measures of motor control in patients with infantile-onset and	Biogen would like to challenge this statement as per the comment relating to page 53 of the NSC review. Biogen have conducted two high-quality RCTs which is a considerable evidence base in an orphan disease, as evidenced by conclusions by the FDA, EMA, SMC, NICE and clinical experts that there is statistically significant value in nusinersen. For an orphan disease such as SMA, where the incidence and prevalence is low and it is impractical to run clinical trials on the same scale as may be feasible for a highly prevalent

	later-onset SMA given nusinersen compared to sham control. However, the evidence base is still small, and there is a lack of data for the long-term effectiveness and safety."	condition such as, for example, type 2 diabetes. We would argue the evidence base is strong to suggest benefit of this therapy. The clinical trial program for nusinersen is very extensive in comparison to clinical trial programmes for other screen rare disease therapies. Moreover, as mentioned as part of the response to page 53, long-term data is now available relating to nusinersen.
Page 58	"Finally, there is 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 are unclear. There is also a lack of evidence on the acceptability of screening to the UK population or the expected uptake of a screening programme."	Biogen would like to challenge this statement. Glascock et al (2018) report a treatment algorithm for infants diagnosed with SMA through newborn screening.(7) Furthermore, Biogen would like to suggest rewording of the statement that the benefits of pre-symptomatic treatment compared to treatment following symptom onset are unclear. As explained in the response to page 14 and summarised again here, the NURTURE clinical trial shows that pre-symptomatic SMA patients greatly benefit from treatment with nusinersen and therefore there is high-quality evidence available that shows the optimal management pathway for SMA patients. A comparison across studies demonstrated greatest improvements in total HINE-2 motor milestones in infants treated with nusinersen in the pre-symptomatic stage of SMA in NURTURE. Furthermore, event-free survival time in nusinersen-treated patients with ≤12 weeks disease duration was longer than in nusinersen-treated patients with >12 weeks disease duration in ENDEAR. This data, along with subgroup analyses of the CHERISH trial and the extension trial SHINE, suggest patients have greater benefits with earlier treatment.(13–16)

Please return to the Evidence Team at screening.evidence@nhs.net by 9th September 2018

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