**National Institute for Health and Care Excellence**

**Single Technology Appraisal (STA)**

**Risdiplam for treating spinal muscular atrophy (ID1631)**

**Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)**

**Please note:** Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

**Comment 1: the draft remit**

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| Appropriateness | Genetic Alliance UK | Because of the size of the potential patient population, and the mode of administration (which will not necessitate that treatment be concentrated in a small number of specialist centres), risdiplam does not meet the strict entry criteria for the HST programme. The previous medicine for multiple subtypes of SMA, nusinersen, was also appraised through the STA route.<br><br>However, SMA is a rare disease, and suffers from the usual challenges in demonstrating the value of a rare disease medicine, such as small and relative short term clinical trials, difficulties collecting quality of life data, etc. The technology appraisal programme is poorly suited for rare disease medicines such as this with small population sizes, relatively immature evidence bases, potential for lifelong use and impacts beyond direct health benefits. The HST programme was developed as a pathway to assess technologies for both rare and very rare conditions, and would be the most appropriate route for evaluation of risdiplam. | Thank you for your comment. Risdiplam does not meet the criteria for the highly specialised technology (HST) programme so will be appraised as a single technology appraisal (STA). No action required. |

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| | Roche Products Ltd | Yes, we consider it is appropriate to refer this topic to NICE for appraisal. | Thank you for your comment. No action required. |
| | SMA REACH UK | Yes. | Thank you. No action required. |
| | TreatSMA | Very Appropriate | Thank you. No action required. |
| | Association of British Neurologists | Yes | Thank you. No action required. |
| | Muscular Dystrophy UK | Yes- this treatment would give people with SMA greater treatment options. | Thank you for your comment. No action required. |
| | Neonatal and Paediatric Pharmacists Group (NPPG) | No comment. | No action required. |
| | Spinal Muscular Atrophy UK (SMA UK) | Highly appropriate given the stage of development of this treatment:<br><br>Clinical Trials and results:<br>Risdiplam is being studied in a broad clinical trial programme in SMA, with patients ranging from birth to 60 years old. One trial includes patients previously treated with SMA-targeting therapies. The clinical trial population represents the broad real-world spectrum of people living with this condition. | Thank you for your comments. No action required. |

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| | | October 2019 Roche's announced data for 45 patients enrolled in their JEWELFISH clinical trial for people aged 6 months-60 years who have previously participated in a trial with *SMN2*-targeting therapies, or olesoxime, or who received previous treatment with nusinersen . A sustained, greater than two-fold increase in median SMN protein versus baseline over 12 months of treatment was demonstrated.<br><br>23rd January 2020 Roche's FIREFISH clinical trial of risdiplam treatment with 21 infants with SMA Type 1 met its primary endpoint. Risdiplam demonstrated statistically significant and medically meaningful motor milestone improvement in these infants i.e. the proportion of infants sitting without support for at least five seconds at 12-months of treatment, assessed by the Gross Motor Scale of the Bayley Scales of Infant and Toddler Development Third Edition (BSID-III).<br>Safety for risdiplam in this study was consistent with its known safety profile and no new safety signals were identified.<br><br>6th Feb 2020 Roche's global placebo-controlled SUNFISH clinical trial Part 2 (n= 180) evaluating risdiplam in people aged 2-25 years who have SMA Type 2 or 3 showed that the change from baseline in the primary endpoint of the Motor Function Measure 32 scale (MFM-32) was significantly greater in people treated with risdiplam, compared to the placebo. The Revised Upper Limb Module also showed an improvement.<br><br>Roche plans to file with the European Medicines Authority in the first half of 2020.<br><br>On 13th January Roche announced its plans for furthering its Global Compassionate Use Access Programme. The company confirmed it will consider individual compassionate use applications made by UK healthcare | |

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| | | professionals on behalf of their patients who have SMA Type 1 and meet the programme's criteria. In the first half of 2020, Roche plans to apply to the Medicines and Healthcare products Regulatory Agency (MHRA) for an Early Access to Medicines Scheme (EAMS) for risdiplam. If accepted, the programme will open to healthcare referrals for those who have SMA Type 2 and meet the programme's criteria.<br><br>These developments indicate a NICE appraisal would be highly appropriate at this time. | |
| Wording | Genetic Alliance UK | The remit (and scope as a whole) should refer to 5q SMA, as individuals with non-5q forms of SMA are not expected to benefit from treatment with risdiplam due to its mechanism of action. | Thank you for your comment. Risdiplam will be appraised for treating spinal muscular atrophy within its marketing authorisation. Please see response to comment in "population" section. No action required. |
| | Roche Products Ltd | Roche agrees with the draft remit in the draft scope document, to appraise the clinical and cost effectiveness of risdiplam within its marketing authorization.<br><br>However, for clarity, the anticipated wording of our marketing authorization is [redacted]<br>We would recommend that the draft remit/appraisal objective is updated to reflect the anticipated marketing authorization wording. | Thank you for your comments. The wording of the remit/appraisal objective and title of the scope have been updated to reflect the clinical trials. Wording has been kept broad to |

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| | | | maintain flexibility during the appraisal. |
| | SMA REACH UK | It does. We understand that the comparison with Nusinersen is not considered in view of the fact that Nusinersen is currently available via a managed access program. Nevertheless we expect that any new drug should have a similar level of efficacy as Nusinersen. As such we would appreciate having more available data on the efficacy of risdiplam either following peer reviewed publications, or as part of the application package | Thank you for your comments. No action required. |
| | TreatSMA | To appraise the clinical and cost effectiveness of risdisplam within its marketing authorisation for treating spinal muscular atrophy in children and adults, including understanding of how such treatment impacts the everyday life of the patients and their families. | Thank you for your comments. No action required. |
| | Association of British Neurologists | The wording misses an essential factor in that spinraza has considerable limitations in its usefulness as a disease modifying treatment due to the need for intrathecal administration whereas risdiplam is orally administered making it very significantly more attractive as a potential treatment | Thank you for comments. The remit is a brief statement outlining the overall objective of the appraisal, and does not discuss further details of the content of the appraisal.<br>No action required. |
| | Muscular Dystrophy UK | Should amend to say that the most severe forms of SMA typically cause death before age 2 year without treatment. | Thank you for your comment. The wording in the background section has been |

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| | | | updated to include 'without treatment'. |
| | NPPG | No comment. | No action required. |
| | SMA UK | It does not refer to all the clinical trials that are underway (see above and below). We understand that more than 400 patients have been / are being treated across all the studies.<br>It does not refer to 5q SMA Type 0 at the most severe end of the spectrum. | Thank you for your comments. Please note that the remit is a brief statement outlining the overall objective of the appraisal and does not discuss further details of the content of the appraisal. The description of the trials in the 'technology' part of the scope has been updated. |
| Timing Issues | Genetic Alliance UK | We understand that the company expects to submit their application to the EMA by the middle of 2020.<br>Risdiplam potentially benefits a broader range of people with SMA than previous treatments, including older patients with more advanced disease. This includes a significant number of patients for whom there is currently no treatment available. Although a compassionate use scheme exists, this currently covers type 1 only. SMA is a progressive condition, and any delays will mean patients' conditions deteriorate unnecessarily. | Thank you for your comments. NICE has scheduled this topic into its work programme and aim to provide draft guidance to the NHS as soon as possible after marketing authorisation. |

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| | | For this reason it is important that patients in England are able to access the treatment as soon as possible after a license is granted. | |
| | Roche Products Ltd | The NICE appraisal of risdiplam should be prioritised to ensure its availability to patients with spinal muscular atrophy (SMA) as early as possible.<br><br>SMA is a rare but serious and life-threatening autosomal recessive neuromuscular disorder, and is the leading genetic cause of death and disability in infants and young children. Whilst disease-modifying treatments for patients with SMA have either been approved or are currently being assessed by the European Medicines Agency (EMA), none of them have been made routinely available through NICE.<br><br>There is therefore a clear need for new treatments that improve or maintain motor, respiratory/bulbar function, and quality of life for patients with SMA. The FIREFISH and SUNFISH studies have demonstrated that risdiplam provides substantial evidence of direct clinical benefit of improved survival and motor milestone achievement in infant-onset SMA patients, and improved motor function in later-onset SMA patients versus natural history. This should be reflected in the urgency for this proposed NICE appraisal.<br><br>Importantly, current and upcoming treatments for SMA require invasive and resource intense procedures of administration, whereas risdiplam, as an orally administered treatment option that can be administered at home, has the potential to broaden access to treatment across the continuum of the SMA patient population. | Thank you for your comments. NICE has scheduled this topic into its work programme and aims to provide draft guidance to the NHS as soon as possible after marketing authorisation. |
| | SMA REACH UK | While currently nusinersen is available via the MAA, it excludes patients with SMA III who are non-ambulant anymore, whose needs would be addressed by risdiplam. In addition, the administration of nusinersen to a proportion of patients with SMA II who have had spinal fusion is complicated, requires complex intervention including exposure to radiations. While the SMA community has initiated the process to identify the best route for intrathecal | Thank you for your comments. No action required. |

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| | | approach for nusinersen for this patient population, including the potential for indwelling catheters, it is also clear that nusinersen is not a straightforward drug to administer in them.<br><br>There are also a small number longer term survivors type 1 for whom nusinersen is not practical but risdiplam could be an option.<br><br>More in general there are a proportion of children and adults with all types of SMA for whom the risk: benefit analysis does not favour use of nusinersen, an additional group for whom technical difficulties make delivery of nusinersen impractical and a group who are currently excluded from treatment with nusinersen under the MAA who may benefit from treatment with risdiplam.<br><br>Risdiplam could represent a much more practical alternative, resulting in a reduced number of hospital appointments for example to access nusinersen via intrathecal injection and less impact on family, school and work life. As indicated above, we would expect that for risdiplam to be considered as an alternative in these patients, there should be clear supportive efficacy data. | |
| | TreatSMA | The urgency of this issue is very high. In SMA, 3-6 months delay getting treatment can mean a loss of function to patient (loss of career or total loss of independence). Within same timeframe, progressive loss in general trunk muscle tone results in scoliosis leading to spinal surgery thus increasing pressure on NHS resources. In cases of SMA type 1 and weaker type 2, there is potential loss of life.<br><br>Whilst there is MAA available to some patients with this condition, significant number is excluded and even those who are included experience difficulty with intrathecal injections thus not able to access Spinraza. | Thank you for your comments. NICE has scheduled this topic into its work programme and aims to provide draft guidance to the NHS as soon as possible after marketing authorisation. |

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| | Association of British Neurologists | Any baby or young person diagnosed with SMA has a very short window of opportunity to prevent the loss of neuronal function and muscle innervation associated with the condition as it may not be reversible. Rapid diagnosis and early treatment are therefore essential particularly in SMA types 1 and 2 and are possibly lifesaving in type 1. If risdiplam is licenced it is urgent that it is considered for approval for use as rapidly thereafter as possible for those babies and infants diagnosed at that time. | Thank you for your comments. NICE has scheduled this topic into its work programme and aims to provide draft guidance to the NHS as soon as possible after marketing authorisation. |
| | Muscular Dystrophy UK | SMA is a progressive condition and the earlier patients are able to benefit from treatment the better their outcomes. Therefore, every effort should be made to start and carry out this appraisal as quickly as possible. | Thank you for your comments. NICE has scheduled this topic into its work programme and aims to provide draft guidance to the NHS as soon as possible after marketing authorisation. |
| | NPPG | No comment. | No action required. |
| | SMA UK | **Very urgent** – without intervention for breathing difficulties, SMA Type 1 typically causes death before age 2 years. SMA Type 2 is also life threatening. All Types of SMA can be severely disabling, impacting on both patient and family.<br><br>As outlined in the remit - for this health technology evaluation, nusinersen, the only possible treatment for those who have SMA Type 1, 2 or 3 and meet the eligibility criteria of the Managed Access Agreement, will not be considered as a comparator. There is no routinely commissioned drug treatment for this condition. | Thank you for your comments. NICE has scheduled this topic into its work programme and aims to provide draft guidance to the NHS as soon as possible after marketing authorisation. |

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| | | The SMA community is closely following developments with this treatment and is anxious that the UK is not, as was the case with nusinersen, one of the last countries in Europe to finally approve managed access to the treatment. This followed a long appraisal process which we hope can be avoided this time. | |
| Additional comments on the draft remit | Genetic Alliance UK | No comment. | No action required. |
| | Roche Products Ltd | No comment. | No action required. |
| | SMA REACH UK | No comment. | No action required. |
| | TreatSMA | No comment. | No action required. |
| | Association of British Neurologists | No comment. | No action required. |
| | Muscular Dystrophy UK | No comment. | No action required. |
| | NPPG | No comment. | No action required. |
| | SMA UK | We suggest any appraisal should include a review of any clinical evidence and clinical advice as to whether risdiplam treatment would be appropriate for infants who are considered to have SMA Type 0. | Comment noted. If evidence allows, and included within the marketing authorisation, consideration will be |

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| | | | given to subgroups based on severity of disease, including SMA type. |

**Comment 2: the draft scope**

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| Background information | Genetic Alliance UK | No comment. | No action required. |
| | Roche Products Ltd | No factual inaccuracies to report. | Thank you for your comment. No action required. |
| | SMA REACH UK | The role of risdiplam in SMN2 splicing regulation is described in general term. The concept is well understood by the specialists working in the field of SMA | Thank you for your comment. No action required. |
| | TreatSMA | In the majority the background information reflects the basic issue and clinically correct. The biochemical processes and clinical meaning is reflected well. However it fails to recognise the effect SMA has on carers and immediate family. Caring for a person with SMA does have significant implications of physical and mental health of carers, which has direct impact on NHS resources. (treating people for back problems and mental burn out). There is also no broad reference to mental health of the patients, carers or families.<br><br>The mental health element of SMA is often neglected, and as with any progressive condition, the uncertainty and unknown impact on patients has a | Thank you for your comments. Please note that this section of the scope is intended to provide a brief summary of the disease and how it is managed, and is not designed to be exhaustive. It includes the following text: “SMA |

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| | | huge mental health aspect. With mental health being a significant concern within the NHS at present we think this should be taken into account.<br>The previous appraisal for SMA treatment has shown significant gaps in understanding of the condition and its impact (clinical and economical) on the patients and NHS. It would be recommended to keep this in mind.<br>Possibly have a patient led forum to familiarise the committee of the impact of SMA. (TreatSMA would be happy to organise for patients to present their view to the committee prior to the appraisal meetings in order to help to educate people involved on the impact of SMA) | also has substantial effects on families and carers, including the impact of caring for the patient, the need for specialist equipment and ongoing emotional, financial and social impacts." No action required. |
| | Association of British Neurologists | Accurate and complete | Comment noted. No action required. |
| | Muscular Dystrophy UK | No comments provided. | No action required. |
| | NPPG | No comment. | No action required. |
| | SMA UK | More accurately:<br>Due to severe and complex symptoms, infants with SMA Type 0 rarely survive the first weeks of life. Without intervention for breathing difficulties, SMA Type 1 typically causes death before age 2 years.<br>Care and management should follow the guidelines agreed by international experts as documented in the International Standards of Care for SMA (SoC). However, there is no directive from NICE/NHS England to ensure this and, due largely to lack of resources, care and management for many falls short of what is recommended. | Thank you for your comments. The background section has been updated to include type 0 SMA and to add that without treatment, severe forms of SMA typically cause death before age 2 years. Please note that this section of the scope is |

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| | | | intended to provide a brief summary of the disease and how it is managed, and is not designed to be exhaustive. |
| The technology/ intervention | Genetic Alliance UK | No comment. | No action required. |
| | Roche Products Ltd | Roche suggests the information below to be added to the description of the technology:<br>• Risdiplam was granted Priority Medicines (PRIME) designation on 16 December 2018 by the EMA, for the treatment of patients with SMA. On 26 February 2019, the European Commission granted Roche orphan designation for risdiplam for the treatment of patients with SMA.<br>• Apart from our studies in Type 1 and Type 2/3 SMA, risdiplam is currently being studied in two additional trials:<br>o JEWELFISH; an open-label, single arm study to investigate safety, tolerability, pharmacokinetics, and pharmacodynamics of risdiplam in adults, children and infants with previously treated SMA<br>o o RAINBOWFISH; an open-label, single-arm clinical study to investigate the efficacy, safety, pharmacokinetics, and pharmacodynamics of risdiplam in infants with pre-symptomatic SMA | Thank you for your comments. The technology/intervention section has been updated to include all of the trials that are taking place. |
| | SMA REACH UK | The description is quite basic; however there are several peer review publication on how this small molecule was identified and on its mechanism of action. These references could be added for completeness | Thank you for your comments. This section of the scope is intended |

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| | | | to provide a brief summary of the technology and any relevant trials, and is not designed to be exhaustive. No action required. |
| | TreatSMA | Yes. It may be useful to cite a number of peer-reviewed publications, but in essence it is accurate. | Thank you for your comments. This section of the scope is intended to provide a brief summary of the technology and any relevant trials, and is not designed to be exhaustive. No action required. |
| | Association of British Neurologists | Accurate but misses an essential factor in that risdiplam is being given to all people with SMA (Sunfish trial) irrespective of their time from diagnosis or whether they have retained ambulation. This is unlike spinraza which is only available to those who are ambulant or have recently lost ambulation; by definition therefore those who are recently diagnosed. | Thank you for your comments. This section of the scope is intended to provide a brief summary of the technology and any relevant trials, and is not designed to be exhaustive. No action required. |

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| | Muscular Dystrophy UK | No comment. | No action required |
| | NPPG | No comment. | No action required |
| | SMA UK | Yes, though not all the trials that are taking place are referenced:<br>FIREFISH: SMA Type 1, 21 children aged 1-7 months<br><br>SUNFISH: SMA Types 2 and 3, Part 1: 51 people aged between 2-25 years. Part 2: 180.<br><br>JEWELFISH: targeted 174 people aged 6 months-60 years who have previously participated in a trial with SMN2-targeting therapies, or olesoxime, or who received previous treatment with nusinersen<br><br>RAINBOWFISH: infants with genetically diagnosed SMA who are not yet presenting symptoms (pre-symptomatic); target of 25 children – the first one recruited in August 2019. | Thank you for your comments. The technology/intervention section has been updated to include all of the trials that are taking place. |
| Population | Genetic Alliance UK | As mentioned above, the population should refer to children and adults with 5q SMA.<br>Risdiplam has also been studied in presymptomatic infants, so it is important that these patients be included in the population under consideration. | Comment noted. The population has been updated to reflect the clinical trials, and has been kept broad to maintain flexibility in the appraisal.<br>If the evidence allows, consideration will be given to subgroups based on severity of |

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| | | | disease (including in people with pre-symptomatic disease and considerations such as age of SMA onset, SMA type and genotype [including SMN2 copy number]). |
| | Roche Products Ltd | The population is appropriately defined in the NICE draft scope. The wording however should be amended to reflect our anticipated marketing authorisation (please refer to response for wording).<br><br>The basis of our evidence submission to NICE will be the efficacy and safety evidence of risdiplam from the broad clinical development program Roche is undertaking. Our clinical development programme includes an SMA population as representative as possible of real-world clinical practice, ranging from infantile-onset SMA to later-onset SMA (age span: 0 to 60 years), with varied baseline characteristics.<br><br>There were no predefined subgroups in our study in Type 1 SMA (FIREFISH). Whilst there were predetermined age subgroups in our Type 2/3 SMA study (SUNFISH), the trial was not powered to demonstrate an efficacy difference for these subgroups.<br><br>Roche does not consider it is appropriate to explicitly consider cost-effectiveness in subgroups of patients from our studies, since (i) subgroup analyses would be associated with small patient numbers, increased uncertainty and lack of robustness in any conclusions, (ii) there is a big remaining unmet need across all types of patients with SMA and (iii) there | Thank you for your comments. The population has been updated to reflect the clinical trials, and has been kept broad to maintain flexibility in the appraisal.<br><br>If the evidence allows, consideration will be given to subgroups based on severity of disease (including in people with pre-symptomatic disease and considerations such as age of SMA onset, SMA type and genotype [including SMN2 copy number]). |

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| | | may be overlap in terms of disease severity between SMA subgroups, making subgroup comparisons not entirely appropriate. | |
| | SMA REACH UK | This drug is being considered for children and adults affected by SMA. In clinical trials there is experience in infants with SMA I; and in children and young adults affected by SMA II and III with age range up to 25 years. SMA 0 have not been studied and considering the mechanism of action of the drug, and the requirement of residual SMN2 gene present (in at least 2 copies, as in the ongoing trial) for this drug to be effective, excluding SMA 0 appears appropriate.<br><br>As the mechanism of action of the drug is on increasing SMN protein production in patients with at least 2 SMN2 copy number, the choice of a broader symptomatic patient population encompassing children and adults is a rationale one.<br><br>Recent data presented at the SMA Europe meeting in France in February 2020 in young adults with SMA (Sunfish study) demonstrated a significant improvement in upper limb function in the treated population, which is expected to improve participation to life of the treated patients.<br><br>There is no information on the older adult patient population (> 25 years) receiving risdiplam as yet. However, based on the pathogenesis of the disease and the mechanism of action of the drug, the older patient population should also respond to therapeutic intervention, along similar lines as the nusinersen adult population, making access to this group important. | Thank you for your comments. The population has been updated to reflect the clinical trials, and has been kept broad to maintain flexibility in the appraisal. |
| | TreatSMA | Population is defined appropriately. However we must keep in mind that clinical studies are carefully constructed, but the actual condition is a spectrum or types, ages and abilities. Therefore the clinical trials do not fully represent the population and there currently no evidence for people over 25 years old. However considering the pathogenesis of the condition and the biochemical mechanism of the technology, it is expected that patients of all | Thank you for your comments. The population has been updated to reflect the clinical trials, and has been kept broad to |

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| | | ages will have various levels of benefit, as long as they have 2 or more copies of SMN2.<br>It is also important to understand that for many the upper limp function improvement will be more significant than ability to stand or walk. | maintain flexibility in the appraisal. |
| | Association of British Neurologists | No. The description “children and adults with SMA” encompasses two distinct populations. There is a difference between the population with pre-symptomatic, newly diagnosed or recently diagnosed SMA and those who have been diagnosed many years ago and who have a resultant longstanding disability. It would be expected that in those with long established condition it may take much longer to manifest any meaningful benefit when compared with those with a new or pre-symptomatic diagnosis.<br>Also, the trials in risdiplam include adults up to age 25years therefore the licence will likely reflect the same age limit rather than all adults with SMA. | Thank you for your comments. The population has been updated to reflect the clinical trials, and has been kept broad to maintain flexibility in the appraisal. |
| | Muscular Dystrophy UK | Given the heterogeneous nature of the condition it should be made clear that this is for children and adults with all types of SMA. | Thank you for your comment. The population has been updated to reflect the clinical trials and has been kept broad to maintain flexibility in the appraisal. |
| | NPPG | No comment. | No action required |
| | SMA UK | This should specify children and adults who have 5q SMA. This includes those with the currently used clinical classification / diagnosis of SMA Types 1, 2, 3 and 4. There should also be appropriate inclusion / reference (as guided by expert clinicians) to infants who have SMA Type 0. | Thank you for your comments. The population has been updated to reflect the clinical trials and has |

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| | | There is no distinct differentiation between types – SMA is a continuum. Age of onset of symptoms guides clinical classification but the impact of the condition varies greatly both between and within these classifications.<br><br>There is consensus (SoC) that use of the observation that someone is a 'non-sitter' 'sitter' or walker' is a more useful guide for appropriate care and management, though this itself fails to address, for example, the impact of SMA on upper body strength, fatigue, fine motor function and the potentially devastating impact of loss of any of these abilities<br><br>It should also clearly include infants with genetically diagnosed 5q SMA who are not yet presenting symptoms (pre-symptomatic) – these infants are being identified for the clinical trial RAINBOWFISH. | been kept broad to maintain flexibility in the appraisal. |
| Comparators | Genetic Alliance UK | No comments provided. | No action required |
| | Roche Products Ltd | Roche agrees with best supportive care being included as the only relevant comparator in the NICE draft scope.<br><br>Roche also agrees with the exclusion of nusinersen, based on the uncertainty in the evidence base to an extent that NICE was unable to make a routine commissioning recommendation. This is also in line with the NICE guide to the methods, which states that therapies with an interim funding recommendation are not considered relevant comparators.<br><br>In addition, an indirect treatment comparison between risdiplam and nusinersen would be challenging, due to the differences in the study populations of these two therapies, as well as the anticipated broader uncertainty in the evidence base. These study differences are especially pronounced in Type 2/3 SMA patients; comparing SUNFISH data to CHERISH data in the absence of a head-to-head trial(s) would be difficult and may not even be possible given significant differences in the study | Thank you for your comments. No action required. |

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| | | populations (age, baseline HFMSE score, presence of scoliosis and severe contractures) between the two studies. | |
| | SMA REACH UK | Nusinersen has been approved for SMA I, II and ambulant III by NHSE and currently most of the children with SMA I receive the treatment.<br><br>In England, the SMA REACH consortium is involved in the management of these patients and collection of its safety and efficacy. So far nusinersen therapy has been prescribed almost exclusively to SMA I children, while preparing the field for the recruitment of SMA II and III, both adults and children.<br><br>Regarding SMA I, SMA REACH has already presented at national and international meetings information regarding the practicalities and efficacy of nusinersen in this patient population, which broadly conform with the efficacy and safety data reported by Biogen in the published ENDEAR clinical trial.<br><br>Regarding Risdiplam in SMA I children, data from the ongoing Firefish study from Roche, presented at several meetings, also indicates a clear drug effect. The order of magnitude of the therapeutic effect appears to be in the same order of magnitude as for nusinersen, but with the available aggregated data it is not possible to unequivocally indicate that one drug is superior to the other one. It will be important to access to more data or to peer reviewed publications to better understand the relative potency of these 2 drugs.<br><br>However, there is an advantage of risdiplam when its mode of administration is compared to nusinersen, in view of the requirement for multiple intrathecal dosage.<br><br>The recent data on Sunfish presented in aggregated form in children and young adults with SMA II and III also demonstrates a clear drug effect. As the inclusion criteria of the patients recruited into this study were very different from the nusinersen RCT on SMA II and SMA III population (Cherish study, in which affected individuals were younger and with a shorter disease duration), | Thank you for your comments. No action required |

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| | | and considering that only aggregated data are available for Sunfish, it is not possible to compare the efficacy of nusinersen and risdiplam in this patient population. More data should be made available to make a comparison based on efficacy. | |
| | TreatSMA | Even though Spinraza is available through the managed access agreement, we do think that best supportive care is the best comparator.<br>Non the less, the clinical evidence has shown that Spinraza and Risdisplam both exhibit similar levels of therapeutically efficacy, even though a direct comparison is not possible at this stage. It is worth noting here that administration of Spinraza via intrathecal injection is significant disadvantage compared to the oral intake of Risdisplam. | Thank you for your comments. No action required. |
| | Association of British Neurologists | Spinraza is not fully approved by NICE but is licenced as a treatment for SMA. To exclude it as a comparator on the technical aspect of its being on a MAA by NICE is unrealistic. Spinraza should be a comparator as the same cost effective assessments are applied to it as to risdiplam. Risdiplam however is an oral treatment whereas spinraza is intrathecal therefore cost-effectiveness alone should not be used to compare the two treatments. Safety and accessibility should also feature. | Thank you for your comments. As nusinersen is available via a managed access agreement, its use is not considered to be embedded in NHS clinical practice because its availability to patients is contingent on further evidence generation and re-appraisal by NICE. Therefore, for the purposes of this appraisal, nusinersen |

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| | | | will not be considered as a comparator.<br>No action required. |
| | Muscular Dystrophy UK | We believe that nusinersen should be used as a comparator as this will now form part of the standard of care for the majority of people with SMA via the Managed Access Agreement, particularly paediatric patients. | Thank you for your comment. As nusinersen is available via a managed access agreement, its use is not considered to be embedded in NHS clinical practice because its availability to patients is contingent on further evidence generation and re-appraisal by NICE. Therefore, for the purposes of this appraisal, nusinersen will not be considered as a comparator.<br>No action required. |
| | NPPG | All relevant comparators included if nusinersen is not being compared.<br>However, we think that it is not appropriate to exclude nusinersen as a comparator, just because it is provided by a managed access agreement and will be re-appraised by NICE. Currently it is a standard of care for this group of patients and so I think it is important to include. | Thank you for your comment. As nusinersen is available via a managed access agreement, its use is not considered to be |

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| | | | embedded in NHS clinical practice because its availability to patients is contingent on further evidence generation and re-appraisal by NICE. Therefore, for the purposes of this appraisal, nusinersen will not be considered as a comparator.<br><br>No action required. |
| | SMA UK | We agree that the 'Best Supportive Care as outlined in the SoC' is the most appropriate comparator for the reasons given in the remit.<br><br>We also note that though 'Best Supportive Care as outlined in the SoC' should be the best alternative care and is a requirement of the nusinersen MAA, this level of care is not available routinely e.g. acute shortage of physiotherapy. Without it, the impact of any treatment is not maximised. | Thank you for your comment. No action required. |
| Outcomes | Genetic Alliance UK | No comment. | No action required. |
| | Roche Products Ltd | Roche broadly agrees with the outcome measures stated in the draft scope but would recommend including the following additional outcome measures:<br><br>• In the motor function outcome, inclusion of age appropriate motor milestones that will be captured in the economic analyses. These include not sitting, sitting, standing, walking (with or without support) | Thank you for your comments. The outcomes have been updated based on consultation comments. |

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| | | • Bulbar function (swallowing, talking)<br>• Frequency and duration of hospitalisation<br>• Independence for daily activities (patient- and/or caregiver- reported)<br>• Health-related quality of life (HRQoL) of carers of individuals with SMA<br>• Impact on work productivity and activity impairment of carers of individuals with SMA<br><br>In terms of specific endpoints used in our clinical studies, Roche would like to highlight that these differ across our trials for different types of SMA patients, and these differences need to be considered during the NICE appraisal process. For motor function, our pivotal study in Type 1 SMA patients used the Bayley scales of infant and toddler development – third edition (BSID-III) as the primary endpoint, while our Type 2/3 study used the motor function measure (MFM) as the primary endpoint. Additional secondary motor function outcomes were also considered, such as Hammersmith Infant Neurological Examination (HINE) in Type 1 patients.<br><br>Regarding HRQoL, the QALY and cost-effectiveness assessment in the Type 1 SMA patient population will be challenging, as there are no validated HRQoL measures for this patient population. In our Type 1 SMA study (FIREFISH), the Infant Toddler Quality of Life (ITQOL) Questionnaire was used. To note, the EQ-5D is not validated in infants. For Type 2/3 SMA patients, our study (SUNFISH) collected EQ-5D to calculate health utility scores for patients, and Work Productivity and Activity Impairment: Caregiver (WPAI:CG) to assess occupational work productivity and activity impairment of parents of individuals with SMA. | |
| | SMA REACH UK | The outcome measures proposed are relevant. We would suggest to add as outcome also feeding issues and bulbar function and their management as these could also be positively affected by risdiplam. | Thank you for your comments. The outcomes have been |

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| | | Some of the suggested outcomes such as fatigue are not well measured in the non-ambulant population and not all HRQOL is suitable for the wide age group involved. | updated based on consultation comments. |
| | TreatSMA | The Real World Evidence should supplement the listed outcomes. Motor function measure is good, but panel must appreciate the impact treatment has on the patients life. Ability to move hand to a shoulder level means ability to use Internet, wheelchair, feeding, cleaning teeth etc. It means more then ability to lift hand above the head. Yet both hand movements have the same motor function score on the scales used.<br><br>Respiratory and feeding issues may also need to be considered.<br><br>Term “health-related” quality of life is too ambiguous and easily brushed aside. The panel needs to understand the impact small improvements or stability can have on patients. The comfort knowing that you are not likely to deteriorate further, or the freedom provided to someone who currently is unable to feed themselves but with treatment may gain that function, it is huge. The panel needs to understand that there is no expectation for huge improvements from patients, but the overall quality of life in terms of self worth and mental health cannot be ignored.<br><br>Finally, there are no outcomes related to mental health. Patients and carers are subject to sever mental strain. Anxiety, fear, depression are a few “norms” for SMA community. Suicides and even murders (infanticides) are known due to emotional and mental pressures. Yet, despite a big drive from NHS these are not listed as outcomes. Real World Evidence could be used here to collect the data or at least understand how this treatment is expected to impact patients and carers. | Thank you for your comments. The outcomes have been updated based on consultation comments. |

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| | Association of British Neurologists | Largely yes although mostly directed at assessing dependent young children. Older children and adults would be better assessed by functional rating scales and assessment of community participation such as attendance at school or employment. A dependency score such as the modified Rankin score may be a useful. | Thank you for your comments. |
| | Muscular Dystrophy UK | The quality of life of families/carers should also be included in order to appropriately capture the broader benefits of treatment. | Thank you for your comment. The outcomes have been updated based on consultation comments. |
| | NPPG | Suggest also to include<br>• swallow, orally fed, feeding tube<br>• awake-assisted ventilation, BiPAP, permanent ventilation etc | Thank you for your comment. The outcomes have been updated based on consultation comments. |
| | SMA UK | We agree with all that are listed but suggest some expansion as follows:<br>• Motor function - including **gross and fine** motor function, **upper and lower limb strength**<br>• Complications of SMA (including for example, scoliosis, muscle contractures, **impact on swallowing and ability to communicate**)<br>Health-related quality of life **for both patient and carer, including mental health and well-being** | Thank you for your comments. The outcomes have been updated based on consultation comments. |
| Economic analysis | Genetic Alliance UK | No comment. | No action required. |

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| | Roche Products Ltd | We would like to highlight that although risdiplam will be appraised through a single technology appraisal (STA), its assessment is anticipated to have several features that are commonly seen in the highly specialised technologies (HST) programme, therefore decision modifiers should be taken into account.<br><br>This was also recognised by NICE in the appraisal of nusinersen in SMA [TA588] (1), where the committee acknowledged the difficulty of appraising drugs for very rare conditions.<br><br>When developing the social value judgements, the Citizens Council considered that rarity alone is not a mitigating factor for accepting high ICERs, and that the committee should consider taking into account other factors such as disease severity in its decision making. In TA588, the committee was aware that SMA is both rare and a very serious condition, and that any treatment benefits are highly valued by patients and families. The committee was mindful during its decision making of the need to consider whether any adjustments to its normal considerations were needed to take into account the rarity and severity of the disease. | Thank you for your comments. No action required. |
| | SMA REACH UK | No comments provided. | No action required. |
| | TreatSMA | Looking at previous appraisal for SMA, it is obvious that QALY/ICERS is lacking capacity to encompass the complexity. Therefore, there must be a mechanism, which allows for flexibility. The mathematical/economical models used can easily fall short of true picture and when assessing the complexity of rare diseases other mechanisms may need to be considered.<br><br>There is no clear understanding on real costs of SMA to NHS or Personal Social Services for the best supportive care. Furthermore, for SMA type 1 the initial costs are very large, but limited to two years (death). This means that | Thank you for your comments. |

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| | | having children with SMA Type 1 living for long is never going to be a cost effective economics. Leniency must be shown here. | |
| | Association of British Neurologists | If the treatment is to be offered to all with a diagnosis of SMA, those with a well established diagnosis of many years may take longer for meaningful benefit to be apparent. | Thank you for your comment. The Guide to the methods of technology appraisal specifies that time horizon should be long enough to reflect all important differences in costs or outcomes between the technologies being compared. |
| | Muscular Dystrophy UK | Given the potential long-term benefits of treatment, the analysis may want to consider differential discounting for costs and benefits | Thank you for your comment.<br>The Guide to the methods of technology appraisal specifies that reference case economic analyses should include discounting for both costs and health effects at the same rate. |
| | NPPG | Supply route needs to be considered as part of access to treatment. We understand that this preparation requires reconstitution and once reconstituted has a limited shelf life of a couple of months and needs fridge | Thank you for your comment. |

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| | | storage. The reconstitution needs to be done within a pharmacy as the bottle is pressurised and it requires a vented safety cabinet with particle filtration and handling precautions. Costs associated with supply to patients e.g. homecare arrangements/costs need to be considered. Presumably initiation / prescribing will be undertaken by named tertiary centres, so in areas with a large geographical area, homecare supply arrangements will be important, as well as how often dosage is reviewed. | Access to treatment based on geography is an implementation issue and cannot be addressed in technology appraisal guidance.<br><br>The Guide to the methods of technology appraisal specifies that reference case economic analyses should include all direct health benefits (for patients and, when relevant, carers) and costs incurred by the NHS and Personal Social Services; consideration will also be given to impacts of the technology beyond direct health benefits including non-health benefits, costs outside the NHS and PSS, and others). |
| | SMA UK | We note the significant difficulties there were with the economic analysis for nusinersen and that the NICE committee's consultation paper (August 2018) | Comment noted. |

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| | | raised concerns that identifying robust utility values in babies and young children is exceptionally challenging.<br><br>**Appropriate Measurement Tools**<br>Though we are aware that there are considerable efforts underway to develop appropriate tools, we draw attention to the flaws measures can present when applied (not specifically to the paediatric SMA population) - as summarised well by Griebsch, I *et al*. Quality-Adjusted Life-Years Lack Quality in Pediatric Care: A Critical Review of Published Cost-Utility Studies in Child Health Pediatrics May 2005, VOLUME 115 / ISSUE 5<br>• Children undergo dramatic changes in growth and function (e.g., mobility, self-care) at different rates, difficulties may arise with attributing improvements to health care interventions rather than to normal development. There is no methodologic guidance about how this should or even might be dealt with.<br><br>• All current generic measures (with the exception of the Health Utility Index Mark 2) are derived from adult populations, and additional attributes that are particularly relevant to child health, including, for example, autonomy, body image, cognitive skills, and family relationships, may not be captured by these measures. Furthermore, no generic instrument for children and infants younger than 5 years is available.<br><br>• Children, particularly young children do not have the cognitive ability to comprehend and complete valuation or even measurement tasks. The implication is that, for very young children, some form of proxy inevitably will be used for measurement tasks, whether this be the clinician or the parent. Although parents may be perceived by economists as the more appropriate source of measurement and/or valuation, the potential for interaction between the utility function of the parent and the proxy (their | The Guide to the methods of technology appraisal specifies that reference case economic analyses should include all direct health benefits (for patients and, when relevant, carers) and costs incurred by the NHS and Personal Social Services; consideration will also be given to impacts of the technology beyond direct health benefits including non-health benefits, costs outside the NHS and PSS, and others).<br><br>Reference case economic analyses should include source data from patient and/or carers for measurement of health-related quality of life. If appropriate, the committee may give consideration to the challenges associated |

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| | | child) for whom he or she is making the measurement/valuation may lead researchers to choose to use clinician judgment to avoid this problem. The issues with this are that: clinicians only see and record a 'snapshot' which may not truly represent the changes taking place and that impact on daily living for both child and parents; measurement tools are insufficiently subtle and limited in their measurements.<br><br>This last point is confirmed in many studies that show this, for example, Srikrishna S, *et al.* (2009*)* Is there a discrepancy between patient and physician quality of life assessment? Neurourol Urodyn. 2009;28(3):179-82. doi: 10.1002/nau.20634.<br><br>We are not aware of appropriate robustly validated patient reported outcome measuring tools that focus on treatment outcomes but consider this a vital element in any economic analysis.<br><br>It is also essential that any measures are considered in relation to the natural history of the condition. Though there is a growing body of evidence on this, this is not always clear cut due to the variation in impact of 5q SMA. Additionally, with sufficient allocation of resources, there are likely to be ongoing changes and improvements to the base case of best supportive care.<br><br>The NICE nusinersen committee (August 2018) further concluded that quantifying carer -related disutilities was extremely difficult.<br><br>A wider perspective<br>We are concerned that an economic analysis should cover all related health and personal health and social services costs including: | with measuring and valuing health-related quality of life in the population under consideration. |

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| | | • the costs caused by the impact of the condition on mental health, emotional and psychological well-being – for the patient and carers<br>• equipment costs and housing adaptations<br>• emergency hospital stays, surgery and clinic time<br>• continuing health care (CHC) cost<br><br>Length of time<br><br>We accept that, due to the length of time the treatment has been trialled, there will be uncertainty as to future long-term outcomes for those treated with this therapy. However, the evidence to date, when other treatments have been assessed and studies and surveys undertaken, clearly indicates that positive treatment outcomes result in these wider costs potentially reducing significantly. We consider it vital that this potential is adequately reflected in the ICER.<br><br>We are also concerned that any model needs to reflect that the health impact is not only on one carer but also on the many e.g. grandparents often play a key role. Also, that due to the 'carer burden' of caring for someone with SMA, that impacts on other caring responsibilities of the carer e.g. a parent who is unable to care for a sick or elderly relative such that their care needs fall to health and personal social services.<br><br>However much effort is made to adjust the ICERs to better reflect evidence and address shortcomings, we suggest that NICE's economic analysis remains fundamentally flawed as it does not reflect the much wider impact in the 'real world' of the costs of the condition and potential benefits of treatment. From our perspective there needs to be a much more holistic approach as only then | |

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| | | can the ICERs really begin to reflect the true potential value of this and any treatment.<br><br>As examples of this 'real world' wider impact of 5q SMA, there are:<br><br>• education costs: requiring Teaching Assistants, school adaptations<br>• work costs: in the long-term loss of potential productivity for the adult with SMA and loss of their contribution to the economy through work / taxes; carers (parents and grandparents) who have to give up work to care for their child; partners who give up work<br>• health and social care costs borne by families: interventions and support paid for by health and social services and included in NICE's model are insufficient for families to manage and are 'topped up' either formally or informally by the family e.g. care hours<br><br>• many equipment and housing adaptation costs are borne by families<br><br>In summary: we strongly suggest that NICE adopts an economic analysis that includes:<br><br>• all these 'real-world' costs that are currently not included in their model<br><br>• all aspects of the health and personal health and social services required to support anyone who has 5q SMA and their family<br><br>• the impact of SMA affecting more than one carer. | |
| Equality and Diversity | Genetic Alliance UK | No comments provided. | No action required. |

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| | Roche Products Ltd | The SMA patient population, for which risdiplam will be a treatment option, includes children and young people, as well as people with disabilities. This will be reflected in our clinical evidence and economic analyses and should also be considered in NICE's decision-making, as per the precedent set in the NICE appraisal of nusinersen in SMA (TA588).<br><br>In TA588, the NICE committee was mindful of the need to consider whether any adjustments to its normal considerations were needed. It discussed the need to balance the importance of improving the lives of children and their families with fairness to people of all ages. It noted NICE's social value judgements: principles for the development of NICE guidance, which emphasise the importance of considering the distribution of health resources fairly within society as a whole, as well as considering factors other than relative costs and benefits.<br><br>In TA 588, the NICE committee also acknowledged that the SMA patient population includes people with disabilities, and acknowledged and considered the nature of the eligible population as part of its decision-making. | Thank you for your comments. This appraisal will consider the technology for treating spinal muscular atrophy, within its marketing authorisation. The committee will give consideration to the impact of disability during the appraisal.<br><br>No action required. |
| | SMA REACH UK | The inclusion of children and adults affected by SMA I; II and III is supported by SMA REACH UK and Adult SMA REACH UK. | Thank you for your comment. No action required. |
| | TreatSMA | The inclusion of adults and children with SMA Type 1, 2 and 3 is supported by TreatSMA and our community. | Thank you for your comment. No action required. |
| | Association of British Neurologists | It is difficult to comment without the licencing authorisation but it appears from the trials that all those diagnosed with 5qSMA have been included irrespective of time from diagnosis. However, the trial has an upper age limit of 25 years and the licence will presumably reflect this and be limited to those under that age. It is difficult to see, if that is the case, how this will avoid | Thank you for your comment. This appraisal will consider the technology for treating spinal muscular |

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| | | creating an inequitable access to the treatment for those around 25 years and over. | atrophy within its marketing authorisation and the committee will consider the evidence that is submitted during the appraisal.<br>As outlined in the Guide to the methods of technology appraisal, when considering subgroups, the NICE Appraisal Committee pays particular attention to its legal obligations on equality and human rights. NICE's equality scheme describes how the Institute meets these commitments and obligations. |
| | Muscular Dystrophy UK | No comments provided. | No action required. |
| | NPPG | No comments provided. | No action required. |
| | SMA UK | The proposed remit and scope appears broad enough to ensure that the following points are all carefully considered:<br><br>It is vital to ensure that all who meet the treatment criteria have equal access, no matter where they live. In view of the fragility of infants with the severest | Thank you for your comments. Access to treatment based on geography is an implementation issue |

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<tr><td></td><td></td><td>SMA, the risk of respiratory infection and the challenges of travelling for many, access should be local. Ideally, the option of the treatment delivered to the person’s home should be available.<br><br>The impact of SMA on each individual varies. Clinical classification by type is not a reliable predictor of the path an individual’s SMA will follow and the impact it will have on their life and the lives of any carers. For example, we support many children who have SMA Type 3 who have lost their ability to walk at an early age and who are very weak and whose day to day lives are not dissimilar to those who are clinically classified as having SMA Type 2. Given this spectrum of 5q SMA and that there are no clear lines between types, we consider all with the condition should have equal opportunity for access, including those who are pre- symptomatic. However, we suggest clinical opinion is needed as to whether this should include infants who have the very severest SMA Type 0.<br><br>The NICE decision re: the nusinersen MAA that excluded so many children and adults with SMA Type 3 has had a devastating emotional and psychological impact on this population who continue to experience the ongoing impact of their condition which causes increasing weakness. We conducted a survey in Jan / Feb 2020 of the impact of the MAA’s exclusion criteria on this group, and their relatives. We had replies from 33 young people and adults (patients) and 22 relatives (replies relating to the 33 and a further 5 patients). The 38 patients (5 ‘proxy’ responses) reported that the decision had impacted them as follows:
<table>
<tr><td></td><td colspan="3">%</td></tr>
<tr><td></td><td>Strongly agree</td><td>Agree</td><td>Total</td></tr>
<tr><td>Made me stressed</td><td>54</td><td>22</td><td>76</td></tr>
<tr><td>Affected me emotionally</td><td>57</td><td>22</td><td>79</td></tr>
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</td><td>and cannot be addressed in technology appraisal guidance.<br><br>This appraisal will consider the technology for treating spinal muscular atrophy, within its marketing authorisation and the committee will consider the evidence that is submitted during the appraisal.<br><br>No action required.</td></tr>
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<tr><td>Made me anxious</td><td>46</td><td>22</td><td>68</td></tr>
<tr><td>Made me angry</td><td>57</td><td>22</td><td>79</td></tr>
<tr><td>Affected my day to day well-being</td><td>42</td><td>14</td><td>56</td></tr>
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Any decision that will exclude part of the 5q SMA population will have a similar adverse impact. We urge NICE to consider this in their deliberations.
It is also vital that NICE is aware that the SMA population has strongly stated that for them treatment is a success if it achieves the outcome stabilisation of the condition. There were 1,327 validated responses from SMA patients/parents to SMA Europe’s survey conducted in July – August 2019 (not yet published). They were asked, ‘If there was a drug to stabilize your current clinical state, would you consider this progress in your opinion?’ 96.7% replied ‘yes’. This was 97.4% of those not receiving treatment (n=846) and 95.1% of those receiving treatment (n=365).
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<tr><td rowspan="2">Other considerations</td><td>Genetic Alliance UK</td><td>No comments provided.</td><td>No action required.</td></tr>
<tr><td>Roche Products Ltd</td><td>In light of the anticipated uncertainties in the evidence base and especially in terms of demonstrating robustness in the long-term outcomes of our economic analyses, Roche considers that a managed access arrangement (MAA) would be an appropriate way to make risdiplam available to patients through the NHS. This would be in line with the precedent set by NICE TA588, in which NICE recommended nusinersen as a treatment option for SMA through a MAA.<br>Roche considers that an MAA recommendation for risdiplam would be appropriate on the basis of:</td><td>Thank you for your comments. No action required.</td></tr>
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| | | • Uncertainties in the clinical trial evidence concerning long-term benefits<br>• Further data becoming available over time through our clinical trial programme<br>• Availability of UK registries SMA REACH (already in place) and Horizon SMA (in development), that can serve as platforms to collect real-world evidence for patients with SMA<br>• Risdiplam is anticipated to meet the criteria for special consideration by NICE<br>• Precedent exists from NICE TA588, indicating that substantial benefits might not be able to be captured by the economic models, including benefits to families and carers | |
| | SMA REACH UK | As there is no data on combinatorial therapy (i.e. risdiplam + Nusinersen), we would not recommend to consider combinatorial therapy. At the same time it can be envisaged that a proportion of patients could transition from Nusinersen to risdiplam treatment. A clear path for which patients could be eligible would be important to be considered. | Thank you for your comments. |
| | TreatSMA | Mental Health<br>Impact on carers and family<br>Real-life understanding of "improvements in functions" | Thank you for your comments. See response to comment in “outcomes” section. “ |
| | Association of British Neurologists | Longer term data collection in those with long standing disease. | Thank you for your comment. |

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| | Muscular Dystrophy UK | The physical, psychological and financial benefits of this treatment to carers/families should be considered in the appraisal. | Thank you for your comment. |
| | NPPG | We think subgroups should be included, particularly based on severity and time since diagnosis. Pre-symptomatic SMA should also be included. | Thank you for your comments. If the evidence allows, consideration will be given to subgroups based on severity of disease (including in people with pre-symptomatic disease and considerations such as age of SMA onset, SMA type and genotype [including SMN2 copy number]). |
| | SMA UK | It is of great concern that the nusinersen MAA has excluded many people living with SMA from the possibility of treatment – with the devastating consequences as outlined above. We are aware that evidence for all treatments is pointing to the earlier it takes place the better the potential outcome. However, there are also positive results in older people and indeed, the longer the duration of treatment the more potential there is for further positive outcomes.<br><br>The **JEWELFISH** clinical trial: for people aged 6 months-60 years who have previously participated in a trial with *SMN2*-targeting therapies, or olesoxime, or who received previous treatment with nusinersen has been designed to include all ages and all 'types' of 5q SMA. As argued above, unless this | Thank you for your comments. This appraisal will consider the technology for treating spinal muscular atrophy, within its marketing authorisation and depending on the evidence presented to the committee. |

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| | | produces clear evidence that the treatment causes a worsening of the condition in a clearly defined sub-group, we strongly suggest that the treatment should be available to all with 5q SMA and, recognising 'the earlier the better', should include pre-symptomatic children. | |
| Innovation | Genetic Alliance UK | No comment. | No action required. |
| | Roche Products Ltd | Despite currently available treatments, the medical need in SMA remains high for alternative, efficacious treatments, which stabilise or improve motor function with a sustainable route of administration.<br><br>Risdiplam is currently the most advanced orally administered treatment option in development for SMA and provides a significant advantage over intrathecal or intravenous injections for patients with SMA. The availability of a convenient oral formulation that can be administered at home would reduce treatment administration burden to the NHS, and also be less burdensome and thus have a significantly positive impact on the lives of both patients and their caregivers. In practical terms, the availability of an orally administered drug should lead to greater adherence, along with access to those for whom other routes of administration can be challenging (e.g., scoliosis and spine surgery for intrathecal administration), and thus has the potential to broaden treatment across the continuum of SMA (i.e., irrespective of the patient's age, type of SMA, or physical status).<br><br>Importantly, orally administered risdiplam crosses the blood-brain barrier to enable distribution throughout the body, increasing levels of functional SMN protein in the CNS, muscle and other peripheral tissues. The totality of currently available efficacy data for risdiplam in patients with infantile-onset and later-onset SMA illustrate a compelling clinical benefit such that improvements in survival, motor milestone achievement and motor function | Thank you for your comments.<br><br>Any innovative aspects of the technology will be considered by the appraisal committee based on evidence presented to it.<br><br>No action required. |

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| | | improvement would not otherwise be expected in the natural disease course for SMA.<br><br>Furthermore, risdiplam achieves steady state in just 2 to 4 weeks, more rapidly than an intrathecally administered antisense oligonucleotide, with the maximum effect on SMN protein obtained within 4 weeks of treatment start; this is important since clinical trial results demonstrate that early treatment leads to better efficacy in SMA patients (2). | |
| | SMA REACH UK | Risdiplam is clearly an innovative drug; it is an oral molecule capable of modifying splicing of SMN2 exon 7 in a very specific fashion, with only a few potential off target splicing issues. Ongoing safety analysis from the current clinical trials has been favourable, with no severe adverse events leading to the discontinuation of risdiplam. As such the available data, together with the oral mode of its administration, and the impact that this more straightforward delivery route has compared to nusinersen, is likely to reduce the burden of the drug delivery both for patients and families and for the NHSE. The reduced burden of administration of risdiplam should therefore have a favourable effect compared to nusinersen on QALY, provided its efficacy is of a similar order of magnitude. | Thank you for your comment. Any innovative aspects of the technology will be considered by the appraisal committee based on evidence presented to it.<br><br>No action required. |
| | TreatSMA | We consider the technology to be HIGHLY innovative and expect it to have SUBSTANTIAL impact on health related benefits for patients and carers. Best supportive care does not adequately meet the medical needs of SMA community. At worst case, the technology will stop the progression of the condition and further deterioration (which is inevitable with best supportive care), at best some or many functions will be restored. This will absolutely be a “step-change” in the management.<br><br>The use of technology is expected to result in substantial and significant health-related benefits that are unlikely to be included in the QALY. As | Thank you for your comments. Any innovative aspects of the technology will be considered by the appraisal committee based on evidence presented to it. |

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| | | explained above in the example of hand movement: hand movement can mean career progression, independence etc…<br><br>TreatSMA has been asking families who are on trial with Risdisplam to keep diaries, which show real world impact on the families involved in the trials. This data of course is not peer-reviewed. Furthermore, we have video-entries of children on the trial doing things which are not included in the assessment. (for example self-transfer from bed into a wheelchair). | |
| | Association of British Neurologists | Yes it is the first oral treatment.<br><br>Additional health related benefits are therefore the access to a treatment without the risk of intrathecal administration. | Thank you for your comment. Any innovative aspects of the technology will be considered by the appraisal committee based on evidence presented to it.<br><br>No action required. |
| | Muscular Dystrophy UK | This treatment provides an innovative alternative to existing treatment for SMA and is administered in a less invasive way (intrathecal injection vs. oral administration) which could benefit patients.<br><br>The QALY does not appropriately capture the benefits (and harms) to patients. There is incomplete understanding from health care professionals of the immense burden of disease and for the implication for parents and carers of children with SMA type 1. Mothers (more often than fathers) will need to turn their child in bed 6-8 times per night, every single night of the year. This leads to consequences in terms of mental and personal health, employment, and wellbeing of the wider family that we do not feel are well captured by the QALY calculations. Whilst the most immediate family affected the most, the | Thank you for your comment. Any innovative aspects of the technology will be considered by the appraisal committee based on evidence presented to it. |

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| | | issue will affect pretty much everybody who is in contact with the family and has a very wide overall impact. | |
| | NPPG | Yes, good promise in the 4 trials | Thank you for your comment. No action required. |
| | SMA UK | Risdiplam is the first orally-administered liquid designed to provide a sustained increase in SMN protein centrally and peripherally, through daily dosing. As such this is a huge step change for SMA making administration possible for all. It also addresses some of the limitations there may be with any treatments that are unable to cross the blood brain barrier.<br><br>Roche has been engaged in surveys and studies of the economic and health related impact of SMA. They have consulted with the SMA Patient community over the structure of these studies and the PAGs have assisted with their dissemination. As such we consider they will be able to present important data. NICE has also gathered a significant amount of data via the appraisal of nusinersen. Though we are aware each appraisal is separate we would hope that relevant aspect of this data (gathered and submitted by patients, clinicians, pharma company) can be referenced. | Thank you for your comments. No action required. |
| Questions for consultation | Genetic Alliance UK | No comments provided. | No action required. |
| | Roche Products Ltd | **Have all relevant comparators for risdiplam been included in the scope?**<br><br>Please see response in “Comparators” section<br><br>**How should best supportive care be defined?**<br><br>As SMA presents with a diverse range of phenotypes of motor impairment and related comorbidities, a multidisciplinary approach is the key element in | Thank you for your comments. |

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| | | the management of SMA patients. SMA is a complex disorder involving different aspects of care and professionals, and each of the aspects should not be dealt in isolation but as part of a multidisciplinary approach. The role of the neurologist / paediatric neurologist in coordinating the various aspects of care, together with the families, is very important. Effective and efficient management of the patient with SMA requires coordination of multiple clinical specialists to address both current concerns and anticipated ones (3).<br><br>A 2018 consensus statement is available regarding international treatment guidelines for patients with SMA, covering and updating topics previously addressed by the International Standard of Care Committee. The 2018 consensus statement is available in two parts: Part 1 provides an update on diagnosis, rehabilitation, orthopaedic and spinal management in SMA, whereas part 2 discusses the pulmonary management, acute care, other organ involvement, ethical issues, medications, and the impact of new treatments for SMA. These guidelines are currently followed by treatment centres in England:<br><br>- Mercuri E, Finkel RS, Muntoni F, Wirth B, Montes J, Main M, et al. Diagnosis and management of spinal muscular atrophy: part 1: recommendations for diagnosis, rehabilitation, orthopedic and nutritional care. Neuromuscul Disord. 2018 Feb (3);<br><br>- Finkel RS, Mercuri E, Meyer OH, Simonds AK, Schroth MK, Graham RJ, et al. Diagnosis and management of Spinal Muscular Atrophy: Part 2: pulmonary and acute care; medications, supplements and immunizations; other organ systems; and ethics. Neuromuscul Disord. 2018 Mar (4)<br><br>**Are the subgroups suggested in "Other considerations" appropriate?**<br><br>A: Please see response in "Population" section | |

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| | | **NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the proposed remit and scope may need changing in order to meet these aims.**<br><br>Please see response in "Equality" section<br><br>**Do you consider risdiplam to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?**<br><br>Please see response in "Innovation" section<br><br>**Do you consider that the use of risdiplam can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?**<br><br>HRQoL assessments are particularly challenging in SMA due to the nature of the condition and the age of the patient population. There are well-documented issues with conceptualising and measuring HRQoL in children and young people (5, 6), which mean that QALYs may not fully capture the value of therapy. Proxy assessments of patient HRQoL may be useful and necessary in this context but may fail to provide a balanced assessment of HRQoL in SMA. In SMA, the situation is further complicated by issues specific to the condition. For example, HRQoL in SMA patients is complicated and motor function may not be the only factor affecting HRQoL (e.g. improvements in motor function may not always lead to predictable improvements in HRQL). For context, there were face validity concerns in several of the utility estimates used in the nusinersen NICE appraisal (TA588) (1).<br><br>In addition, based on what is known about the disease and the burden on carers and families, it is acknowledged that a utility does not adequately | |

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| | | capture the impact on carers and that this approach is likely to understate the benefits of risdiplam. This was also evident as part of the NICE appraisal of nusinersen (NICE TA588)<br><br>**To help NICE prioritise topics for additional adoption support, do you consider that there will be any barriers to adoption of this technology into practice? If yes, please describe briefly?**<br><br>We do not anticipate any barriers for the adoption of risdiplam in clinical practice.<br><br>As an orally administered treatment option that can be administered at home and used for a life-long condition, risdiplam has the potential to broaden access to treatment across the continuum of the SMA patient population (i.e., irrespective of the patient's age, type of SMA, or physical status). Risdiplam therefore provides a potential new treatment option that potentially addresses barriers or equality concerns with respect to access to therapy for all patients with SMA.<br><br>**NICE intends to appraise this technology through its Single Technology Appraisal (STA) Process. We welcome comments on the appropriateness of appraising this topic through this process.**<br><br>Roche agrees with the appraisal of this technology through the NICE STA Process<br><br>1.National Institute for Health and Care Excellence. Nusinersen for treating spinal muscular atrophy [TA588]. 2019. | |

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| | | 2.Dangouloff T, Servais L. Clinical Evidence Supporting Early Treatment Of Patients With Spinal Muscular Atrophy: Current Perspectives. Ther Clin Risk Manag. 2019;15:1153-61.<br><br>3.Mercuri E, Finkel RS, Muntoni F, Wirth B, Montes J, Main M, et al. Diagnosis and management of spinal muscular atrophy: Part 1: Recommendations for diagnosis, rehabilitation, orthopedic and nutritional care. Neuromuscul Disord. 2018;28(2):103-15.<br><br>4.Finkel RS, Mercuri E, Meyer OH, Simonds AK, Schroth MK, Graham RJ, et al. Diagnosis and management of spinal muscular atrophy: Part 2: Pulmonary and acute care; medications, supplements and immunizations; other organ systems; and ethics. Neuromuscul Disord. 2018;28(3):197-207.<br><br>5.Matza LS, Swensen AR, Flood EM, Secnik K, Leidy NK. Assessment of health-related quality of life in children: a review of conceptual, methodological, and regulatory issues. Value Health. 2004;7(1):79-92.<br><br>6.Gerharz EW, Eiser C, Woodhouse CRJ. Current approaches to assessing the quality of life in children and adolescents. BJU Int. 2003;91(2):150-4. | |
| | SMA REACH UK | No comment. | No action required. |
| | TreatSMA | No comment. | No action required. |

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| | Association of British Neurologists | “Best supportive care” will be different depending on the age of the patient but is defined in guidelines. It is well recognised however that patients rarely are able to access best supportive care as this should include such things as psychological support which is patchy in its availability. | Thank you for your comments. No action required. |
| | Muscular Dystrophy UK | No comments provided. | No action required. |
| | NPPG | **How should best supportive care be defined?**<br>Supportive care must include hospitalisation rates<br>**Are the subgroups suggested in ‘other considerations appropriate? Are there any other subgroups of people in whom risdiplam is expected to be more clinically effective and cost effective or other groups that should be examined separately? Would it be appropriate to consider subgroups based on severity of symptoms or time since diagnosis?**<br>Yes, patients with spinal complications i.e. surgery, scoliosis<br>**Do you consider that the use of risdiplam can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation? Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits.**<br>4 clinical trials | Comments noted. If the evidence allows, consideration will be given to subgroups based on severity of disease (including in people with pre-symptomatic disease and considerations such as age of SMA onset, SMA type and genotype [including SMN2 copy number]). |
| | SMA UK | **Do you consider that there will be any barriers to adoption of this technology into practice?**<br>We cannot see there being any barrier caused by the method of administration. | Thank you for your comments. |

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| | | We imagine clinicians caring for patients who do not have access to nusinersen will welcome this treatment as will the patients themselves.<br>One barrier may be the lack of reliable comparative information about the efficacy of the various possible treatments. This would make it difficult for a patient / carer faced with more than one option to make a choice. The best possible comparative information will need to be developed as quickly as possible to assist patients and clinicians.<br>As always, price could be a barrier if this treatment is appraised via an STA route designed for common conditions - with its low-cost effectiveness threshold.<br>**Suitability of a Single Technology Appraisal Process**<br>There is still a binary choice of an STA versus an HST route. The higher cost effectiveness threshold of the HST would be more appropriate for what is a rare condition. However, this is a treatment that is potentially suitable for all with 5q SMA therefore it does not meet the extremely rigid and low HST barrier in terms of population numbers. Similarly, as access to treatment will not need to be via a very small number of treatment centres, this criterion will not be met. In view of this and that nusinersen was appraised via an STA route, the choice has to be an STA process. However, we urge the NICE committee when it meets to be as flexible as possible in its appraisal. We continue to hope that we will soon see a change to this rigid binary system. | |
| Additional comments on the draft scope | Genetic Alliance UK | No comment. | No action required. |
| | Roche Products Ltd | No comment. | No action required. |
| | SMA REACH UK | No comment. | No action required. |

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| | TreatSMA | No comment. | No action required. |
| | Association of British Neurologists | No comment. | No action required. |
| | Muscular Dystrophy UK | No comment. | No action required. |
| | NPPG | Appraisal should be undertaken with similar criteria that NICE used for nusinersen. | Thank you for your comment. No action required. |
| | SMA UK | No comment. | No action required. |