Multiple technology appraisal (MTA) commission by the NIHR Evidence Synthesis Programme on behalf of the National Institute for Health and Care Excellence – final protocol

Title of project: Spinal muscular atrophy - nusinersen (MAA review of TA588) and risdiplam (MAA review of TA755) [ID6195] – Final Protocol

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Produced by Warwick Evidence

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Date completed 16/01/2024

Glossary

AE	Adverse event
AR	Assessment report
BNF	British National Formulary
BSC	Best supportive care
CEA	Cost-effectiveness analysis
CHEERS	Consolidated health economic evaluation reporting standards
EAG	Evidence assessment group
eMIT	Electronic marketing tool
HINE-2	Hammersmith Infant Neurological Examination Module 2
HRQoL	Health-related quality of life
ITC	Indirect treatment comparison
LYG	Life-year gained
MAA	Managed Access Agreement
MAIC	Matching-adjusted indirect comparison
MTA	Multiple Technology Appraisal
MFM	Motor function measure
NA	Not applicable
NHB	Net health benefit
NHS	National Health Service
NMA	Network meta-analysis
NR	Not reported
NICE	National Institute for Health and Care Excellence
PPI	Patient and public involvement
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
PROM	Patient reported outcome measure
PSA	Probabilistic sensitivity analysis
PSSRU	Personal social services research unit

PSW	Propensity score weighting
QALY	Quality-adjusted life year
SAE	Severe adverse event
SLR	Systematic literature review
SMA	Spinal muscular atrophy
TA	Technology appraisal
WHO	World Health Organization

1 Plain English Summary

Spinal muscular atrophy (SMA) is an uncommon condition that causes muscle weakness. Over time SMA leads to problems with the function of the spinal cord and loss of movement in the body. SMA is usually caused by faults in the persons genes and affects the motor neurones. These are the cells in the brain that allow people to crawl and move. Motor neurones also support movement of the arm, head and neck, and include swallowing and breathing. Across the world SMA affects one to two people in every 10,000 people. Most recent information from the UK suggests that approximately 70 people were born with SMA in 2021. Type 1 SMA can develop between 2 to 6 months of age, but people can be diagnosed later in life (Types 2, 3 and 4 SMA). SMA causes much disability and can result in death. SMA affects families and carers, including the impact of caring for the patient. There is often a need for specialist equipment and ongoing emotional, financial, and social support for people with SMA.

There is a new treatment available for people with SMA. It is called onasemnogene aberparvovec. This treatment is used for certain types of SMA, known as Type 1 SMA and for pre-symptomatic SMA. It can be used for babies who are 6 months or younger. Or in babies aged 7 to 12 months when their treatment is agreed by a national team of clinical experts. Onasemnogene aberparvovec is a gene therapy which means it works to correct the faulty genes in the patient with SMA. There are two other treatments available for people with all SMA types. These are called nusinersen and risdiplam and are not gene therapies. These treatments appear to give benefits to patients in the short term, but we are uncertain of their longer-term benefit. To help us to understand long term benefit of these treatments a treatment funding scheme was introduced. In this scheme, known as a Managed Access Agreement, the two treatments (nusinersen and risdiplam) were made available to patients in the NHS and longer-term data was collected to examine if the treatments continued to work.

In addition to examining the data from the treatment funding scheme, we will use a method called systematic review, to examine all scientific information about the treatments. Using both types of data will aim to understand the long-term benefits, and harms, of the treatments available for SMA. It is important that medical treatments also represent good value for money for the NHS. Therefore, we perform scientific methods to examine the value for money of medicines, this is known as health economics and economic modelling. The results from an economic analysis help health and care decision makers to decide how to spend limited healthcare resources. In this study, the economic models will compare the different treatments and use cost information from many sources, to estimate the costs and

benefits of the treatments. The results of the economic modelling will be presented as a quality-adjusted life year (QALY). In the UK, this is the standard measure for valuing healthcare treatments over a person's lifetime. The QALYs help decision makers to understand the additional years a patient might gain from taking treatments for SMA such as nusinersen or risdiplam. It also provides information on the quality of the person's life during those years. In a previous study, both nusinersen and risdiplam were considered to offer good value for money for the NHS. It is important to update this economic modelling using the longer-term data we have collected. The results of this study will allow us to understand if these treatments continue to offer good value for money as well as providing benefits to patients.

In this study, we will examine the patient benefit (known as clinical effectiveness) and value for money (known as cost-effectiveness) of the two treatments, nusinersen and risdiplam. We will compare this information to the standard care patients would receive if no treatment was given (known as best supportive care) and the new gene therapy onasemnogene abeparvovec. The results of the study will be used to help the health and care decision makers decide whether all the treatments can be made available for patients of different types.

2 Background

2.1.1 Introduction

This Multiple Technology Appraisal (MTA) is appraising the clinical and cost-effectiveness of the use of nusinersen and risdiplam for treating spinal muscular atrophy, versus established clinical management, best supportive care, and each other. Onasemnogene abeparvovec will be compared in children 12 months and under.

Guidelines for the treatment of spinal muscular atrophy in the UK come from the International Standards of Care for SMA by Spinal Muscular Atrophy UK.[1]

2.1.2 Disease overview

Spinal muscular atrophy (SMA) is a rare genetic disorder characterised by degeneration of alpha motor neurons in the spinal cord, resulting in progressive muscle atrophy, muscle weakness and paralysis.[2] The most common type of SMA is caused by a defect in the survival motor neuron 1 (SMN1) gene.[2] SMN1 is estimated to be found in approximately 1 in 11,000 births, making it the most common inherited cause of mortality in infants.[3]

SMA most commonly affects motor neurons responsible for walking, crawling, arm, head and neck movement, swallowing and breathing.[4] The symptoms and severity of SMA vary greatly, and SMA is therefore classified into a series of types, decreasing in severity, based on the age of symptom onset, and the best motor function achieved.[1] According to Standards of Care guidance, Type 1 (in infants younger than 6 months) is characterised by an inability to sit or roll independently, Type 2 (7 to 18 months) is characterised by an ability to sit, but not walk independently, Type 3a (18-36 months) and Type 3b (3-18 years) reflects an ability to walk, although this ability may be lost over time, and Type 4 (over 18 years) is characterised by mild walking and motor difficulties.[1] An additional Type (Type 0) occurs antenatally or after birth, resulting in the most severely affected individuals. Prognosis within this group is poor, with death often occurring within weeks.[1, 5] Most SMA patients suffer from Type 1.[6]

Table 1: Spinal muscular atrophy types

Type	Age of onset	Maximal motor milestone	Motor ability and additional features	Prognosis[c]
SMA 0	Before birth	None	Severe hypotonia; unable to sit or roll[a]	Respiratory insufficiency at birth; death within weeks
SMA 1	< 6 months	None	Severe hypotonia;	Death/ ventilation by 2 years

			unable to sit or roll[b]	
SMA 2	6- 18 months	Sitting	Proximal weakness; unable to walk independently	Survival into adulthood
SMA 3 **3a** **3b**	 18- 36 months 3-18 years	 Walking Walking	May lose ability to walk	Normal life span
SMA 4	>30 years or 10– 30 years	Normal	Mild motor impairment	Normal life span

[a] Need for respiratory support at birth; contractures at birth, reduced foetal movements.
[b] Joint contractures present at birth; may achieve head control.
[c] Prognosis varies with phenotype and supportive care interventions.

Table adapted from Farrar et. Al (2017) and SMA UK (2023)[1, 5]

2.1.3 Current treatment pathway

Current treatment for SMA includes onasemnogene abeparvovec, a gene therapy administered intravenously to children 12 months or younger, where a mutation in the SMN1 gene is present, and a diagnosis of type 1 SMA has been given. At the time of submission for risdiplam, onasemnogene abeparvovec was not established clinical management in the UK.[7]

Best supportive care (BSC) requires a tailored multidisciplinary approach. This includes no active disease modifying treatment, but instead monitors and supports patients in the treatment of symptoms. In recent years, SMA care has improved, with advancements on ventilatory and feeding support and palliative care.[8] Best supportive care often has limited improvement and mortality rates remain high.[9]

Nusinersen is available under a MAA for pre-symptomatic and symptomatic patients with 5q SMA who have infantile (type 1) or later onset (those likely to develop type 2 or 3). Nusinersen is administered as an intrathecal bolus injection over 1–3 minutes, via lumbar puncture.[10] Treatment is continuous as it is a life-long condition.

Risdiplam is available under a managed access agreement (MAA) for people with SMA. Risdiplam is administered orally once daily using a re-usable oral syringe. Treatment is continuous as it is a life-long condition. Risdiplam is an SMN2 mRNA splicing modifier, which increases the expression of functional SMN protein from the SMN2 gene.[7]

2.1.4 Review of each TA (TA588 and TA755)

As outlined in Section 3, this MTA is a review of two previous technology appraisals (TA), nusinersen for treating SMA (TA588) and risdiplam for treating SMA (TA755).[11, 12] We provide a brief summary of these appraisals below and MAA criteria.

2.1.4.1 Nusinersen for treating spinal muscular atrophy TA588 Published: 24 July 2019

Nusinersen (Spinraza, Biogen Idec) has a marketing authorisation for *'the treatment of 5q spinal muscular atrophy'*. The NICE TA for this technology states that nusinersen is recommended as an option for treating 5q spinal muscular atrophy (SMA) only if "*people have pre-symptomatic SMA, or SMA types 1, 2 or 3*" and the conditions of the MAA are followed (*see* Section 2.1.4.1.1).[11] These recommendations were made because at the time of the appraisal, there was no long-term evidence to resolve the uncertainty of long-term benefits of nusinersen. Consequently, the cost-effectiveness estimates presented in TA588 were higher than what NICE usually considers a cost-effective use of NHS resources. However, the committee concluded that nusinersen had demonstrated the potential to be cost-effective. The lack of longer-term evidence results in estimates that are difficult to interpret. TA588 also highlights the difficulty in clearly distinguishing between the SMA subtypes, and the difference in what can be achieved for these various patients without nusinersen.[11]

2.1.4.1.1 Criteria and data collection specified in the MAA

The MAA[13] includes i) statement that sets out the clinical criteria for starting and stopping treatment with nusinersen and ii) a data collection plan to evaluate the performance of nusinersen over five years.

This focuses on a narrower subset of the marketing authorisation population: patients with early onset (type I), later onset (types II and III) SMA and presymptomatic patients (patients genetically destined to develop SMA). The TA588 company submission submitted evidence which did not include cover type 0 (severe infantile SMA) or type IV (symptom onset in adulthood) SMA patients. Patient entry criteria (aligns to Type 1, 2, 3, and presymptomatic) for the MAA include:[13]

- *"Patient has a confirmed genetic diagnosis of 5q autosomal recessive SMA and meets one of the following criteria:*
    - *Has SMA type 1, 2, or 3.*

    - *Pre-symptomatic of SMA and has one to four SMN2 copies.*
- *Nusinersen is used as a monotherapy.*
- *Must not have had successful treatment with onasemnogene abeparvovec.*
- *No permanent ventilation (≥16 hours/day for 21 consecutive days in the absence of acute reversible infection)/ tracheostomy requirement at baseline. Patients who do not meet this criterion but otherwise meet the eligibility criteria should be discussed with the NHS England Clinical Panel.*
- *Intrathecal injection must be technically feasible in the opinion of the treating clinician and not contraindicated.*
- *Must not have received spinal fusion surgery following a diagnosis of scoliosis which, in the opinion of the treating clinician, prohibits safe administration of nusinersen."*

The MAA requires that data should be collected on all 5q SMA patients regardless of whether they meet the MAA criteria. Data collection includes clinical data, patient reported outcome measures (PROMs) data, and resource utilisation data (See Table 2).

Table 2: Data collection specified in the MAA

Data type	Detail	Source
Clinical data	• all fields linked to the NICE appraisal uncertainties and available in the SMA REACH database. • SMA REACH Registry • A minimum of two data entries per patient per year for each mandated field after the initial baseline assessment • Any two entries need to be at least 4 months apart. Two data points a year will allow to counteract the outcome variability due to "off" days and acute, reversible illness. The time spacing is designed to coincide with either routine 6 monthly follow up clinic appointments or 4 monthly maintenance doses. • Clinical endpoints to be evaluated will be determined by patient motor milestones at initiation of therapy and patients age, o Survival o Ventilation/respiratory events (e.g., infections) o Motor function o Scoliosis surgery	MAA appendix E Disease specific database which collects data from all available SMA patients independent of their treatment regimen. SMA REACH UK collects data from routine clinical visits with data uploaded by a patient's healthcare team. It is hosted on the Certus platform and coordinated by the UCL Institute for Child Health. MAA appendix C MMA MAA appendix D
PROMS data	• Biogen contracted the UK SMA Patient Registry to collect patient-reported data from individuals with SMA. • The SMA Patient Registry is an established database. • Data is captured on the Munich Platform, hosted by AIMES Management Services and the patient registry is coordinated from John	Biogen is responsible for commissioning separate agreements which will ensure that data is collected during the Term of the MAA period on patient and carer quality of life.

Data type	Detail	Source
	Walton Muscular Dystrophy Research Centre, Newcastle.	
Resource utilisation data	• Use of healthcare resources in terms of patient admissions, medical investigations and therapies, medical equipment and personnel associated with the management of the SMA patients.	Not collected through SMA REACH. Anticipated that the data will be collected by annual or biannual surveys
MAA, Managed Access Agreement; PROMS, patient reported outcome measures; SMA, spinal muscular atrophy; UCL, University College of London		

2.1.4.2 Risdiplam for treating spinal muscular atrophy TA755 Published: 16 December 2021 Updated: 15 December 2023

Risdiplam (Evrysdi, Roche) has a marketing authorisation in the UK for the treatment of 5q spinal muscular atrophy (SMA) in patients with a clinical diagnosis of SMA Type 1, Type 2 or Type 3 or with one to four SMN2 copies.[12] The NICE TA for this technology states that risdiplam is recommended as an option for treating 5q spinal muscular atrophy (SMA) in people of all ages with a clinical diagnosis of SMA types 1, 2 or 3 or with pre-symptomatic SMA and 1 to 4 SMN2 copies. It is recommended only if the conditions of a managed access agreement are followed.[12]

The committee state that there is no direct evidence comparing risdiplam with usual care for type 1 SMA, and that at the time of recommendation, there was no long-term evidence of benefits. The committee also state that the cost-effectiveness estimates are higher than what NICE usually considers an acceptable use of NHS resources. However, because of the unmet need for effective treatments for SMA, risdiplam was recommended via MAA to enable data collection to address uncertainties in the evidence.[12] Additional clinical uncertainty include uncertainty associated with inclusion of caregiver utility values and the approach to account for risdiplam's additional benefits that were not captured in the clinical outcomes and economic model.

2.1.4.2.1 Criteria and data collection specified in the MAA

The MAA includes the following patient eligibility criteria;

- Patient meets one of the following criteria:
    - Clinical diagnosis of SMA type 1, 2, or 3

- Pre-symptomatic of SMA and has been confirmed to have SMA via genetic testing and has one to four SMN2 copies

- Risdiplam is used as a monotherapy.
- Must not have had successful treatment with onasemnogene abeparvovec.
- No permanent ventilation (≥16 hours/day for 21 consecutive days in the absence of acute reversible infection)/ tracheostomy requirement at baseline.
- Mandated data items have been collected prior to starting treatment within this MAA (see Table 3).
    - Patients who started treatment for SMA prior to the MAA were not required to repeat an assessment if a previous assessment has captured all mandated data items within the last 6 months.
- Patient/carer has signed the MAA and agreed to the associated monitoring, clinical assessments and sharing of data for the purpose of the MAA.
- Clinician confirms they:
    - will submit data to SMA REACH UK as set out in the DCA.
    - have made the patient/carer aware that there are other treatments for SMA, which may be more suitable for that patient.
    - confirm annually, via completion of an addition Blueteq form, that the patient continues to receive benefit from treatment.

The committee concluded that further data collection during the MAA could possibly resolve the uncertainties that were identified during the appraisal. The MAA specifies the source of data collection outlined in Table 3.

Table 3: Primary and secondary sources of data collection

Name	Additional evidence	Comment
Primary Sources		
SUNFISH	FIREFISH and SUNFISH trials will provide long-term clinical effectiveness data of risdiplam, including: • Survival, the attainment of motor milestones, a risdiplam specific treatment plateau, gains in upper limb	Safety and efficacy of risdiplam (2:1 risdiplam:placebo) SMA 2 and SMA 3 (children and young adults; 2-25 years) primary endpoint - change from baseline in MFM32 score; secondary endpoints - motor function (RULM; HFMSE) and Patient Reported Outcomes (SMAIS -

Name	Additional evidence	Comment
	function, changes in respiratory function, adverse events, utility values and treatment discontinuation. • Data are critical for informing an economic model for assessing the cost-effectiveness of risdiplam versus best supportive care. • data on pre-treated and pre-symptomatic patients, respectively.	SMA Independence Scale). Safety data including AEs and SAEs
FIREFISH		Safety and efficacy of risdiplam SMA 1 (infants; 1-7 months primary endpoint - infants sitting without support for at least 5 seconds as measured by the BSID-III; secondary endpoints - motor function (BSID-III; HINE-2; CHOP-INTEND), survival, hospitalisations, bulbar function. Safety data including AEs and SAEs.
SMA REACH UK	SMA REACH UK will collect the following outcomes through its registry: • patient & assessment details • SMA type, including molecular genetic diagnosis • cause of death in event of mortality • nutritional status, including swallowing problems • scoliosis • motor function using SMA validated scales appropriate for the level of function of the patient • fractures • ventilation / respiratory events; respiratory function tests • treatment use and outcomes, including reasons for treatment discontinuation	pre-existing disease specific database which collects data from all available SMA patients independent of their treatment regimen. SMA REACH UK collects data from routine clinical visits with data uploaded by a patient's healthcare team. It is hosted on the Certus platform and coordinated by the UCL Institute for Child Health.
Patient and carer quality of life		During the period of the MAA the company is responsible for collecting further data that describe patient's and caregivers' quality of life, physical functioning and other outcomes.

Name	Additional evidence	Comment
Secondary Sources		
RAINBOWFISH		(<6 weeks old) assesses the safety and efficacy of risdiplam in infants with SMA who are not yet showing symptoms. primary endpoint - to evaluate the efficacy of risdiplam in infants with two SMN2 copies and CMAP amplitude ≥1.5 mV at baseline as determined by: • the proportion of infants sitting without support for 5 seconds after 12 months on treatment as assessed by the BSID-III Gross Motor scale. Secondary endpoints - proportion of infants developing clinically manifested SMA; time to death; time to death or permanent ventilation; proportion of infants alive; proportion of infants alive without permanent ventilation; motor function (BSID-III; CHOP-INTEND; HFMSE); change from baseline in growth measures; nutritional status; change from baseline in CMAP amplitude; SMN protein and mRNA levels; PK and safety data
JEWELFISH		(children and adults; 6 months - 60 years) assesses the safety and tolerability of risdiplam in people who have previously received SMA treatments (pre-treated patients). primary endpoints - safety (incidence and severity of AEs, abnormal laboratory values, ECGs and vital signs), and tolerability and PK parameters, including mean plasma concentration, maximum concentration, area under the curve and minimum concentration of risdiplam and metabolites. Efficacy endpoints are exploratory endpoints
AE, adverse event; ECG, electrocardiogram; SAE, severe adverse event		

2.1.5 Decision problem TA588 and TA755

We provide an overview of the CS decision problem from TA588 and TA755 in Table 4 and Table 5, respectively. A comparison of these original decision problems and the decision problem for this MTA is provided in appendix 10.1.

Table 4: Decision problem: Nusinersen (reproduced from EAG report for TA588)

	Final scope issued by NICE	Decision problem addressed in the CS	EAG comment on rationale if different from the final NICE
Population	People with 5q SMA	Pre-symptomatic and symptomatic people with 5q SMA who have infantile onset (those who have or are most likely to develop type I) or later onset (those who have or are most likely to develop types II and III) SMA	The proposed population is narrower than the marketing authorisation (which includes all patients with 5q SMA) because the evidence base on nusinersen is limited to patients with pre-symptomatic and symptomatic infantile onset and later onset SMA
Intervention	Nusinersen	Nusinersen	N/A
Comparator(s)	Best supportive care	Sham procedure and standard of care treatment	Biogen consider that the most appropriate comparator is sham procedure (administered by lumbar puncture prick), as no disease-modifying therapies (other than nusinersen) are approved or routinely

Outcomes	The outcome measures to be considered include: • Motor function (including, where applicable, age appropriate motor milestones) • Respiratory function • Complications of SMA (including, for example, scoliosis and muscle contractures) • Need for non-invasive or invasive ventilation • Stamina and fatigue • Mortality • Adverse effects of treatment • HRQoL	The outcome measures to be considered include: • Motor function (including, where applicable, age appropriate motor milestones) • Event-free survival (time to death or permanent assisted ventilation) and overall survival • Respiratory function • Need for non-invasive or invasive ventilation • Mortality • Adverse effects of treatment • HRQoL	Complications of SMA (including, for example, scoliosis and muscle contractures), and stamina and fatigue, are not included as these outcomes were not collected in the pivotal clinical trials.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per QALY. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and personal social services perspective.	The economic analysis considers 2 *de novo* models to assess the cost-effectiveness of nusinersen using motor milestones health states – 1 relating to infantile onset SMA and the other to later onset SMA. The pre-symptomatic health state is being developed but could not be modelled in time for submission.	N/A

Subgroups to be considered	Consideration will be given to subgroups based on severity of disease (including considerations such as age of SMA onset, SMA type and genotype [including *SMN2* copy number]). Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.	The pivotal trials in infantile onset (ENDEAR) and later onset SMA (CHERISH) included pre-specified subgroups based on disease duration and age at symptom onset. For infantile onset SMA patients the economic analysis has evaluated the subgroups based on age at onset of SMA symptoms and disease duration (>12 weeks and ≤12 weeks) from the ENDEAR trial For later onset SMA patients, subgroup analysis has not been conducted in the economic analysis due to the small subgroup sample sizes within	N/A
Special considerations including issues related to equity or equality	NR	N/A	N/A
CS, company submission; HRQol, health-related quality of life; N/A, not applicable; NR, not reported; QALY, quality-adjusted life year; SMA, spinal muscular atrophy; SMN2, survival motor neuron 2			

Table 5: Decision problem: Risdiplam (reproduced from EAG report for TA755)

	Final scope issued by NICE	Decision problem addressed in the CS	EAG rationale if different from final NICE scope
Population	People with spinal muscular atrophy	As per NICE scope	N/A
Intervention	Risdiplam	As per NICE scope	N/A
Comparator(s)	Best supportive care	As per NICE scope	N/A
Outcomes	• Motor function (including, where applicable, age-appropriate motor milestones such as sitting, standing and walking) • Bulbar function (including, for example, swallowing and ability to communicate) • Frequency and duration of hospitalisation • Respiratory function • Complications of SMA (including, for example, scoliosis and muscle contractures) • Need for non-invasive or invasive ventilation • Stamina and fatigue • Mortality • Adverse effects of treatment • HRQoL	The CS broadly aligns with the final scope issued by NICE. Not all outcomes listed in the final scope are, however, explicitly used in the economic models. Type 1 SMA: Health state occupancy in the economic model was based on motor milestone achievement using HINE-2, similarly to TA588. A separate health state for patients on permanent ventilation was included, as permanent ventilation is associated with additional costs and a more severe prognosis for patients with SMA type 1. Additional clinical outcomes from the FIREFISH study will also be used to inform the economic model, such as event-free survival and respiratory outcomes. Type 2/3 SMA: Health state occupancy in the economic model was based on motor	Effort to simplify the model structure – based on previous economic models and clinical expert opinion - and avoid the use of additional assumptions where possible

	Final scope issued by NICE	Decision problem addressed in the CS	EAG rationale if different from final NICE scope
		milestone achievement using MFM, the primary endpoint of the SUNFISH study. The MFM was selected as a primary endpoint on the basis that it can offer sufficient gradation in the assessment of functional abilities, to fully enable assessment of treatment efficacy in a broad population of Type 2 or 3 SMA patients, like the one included in SUNFISH. Additional clinical outcomes from the SUNFISH study will also be used to inform the economic model.	
Economic analysis	The cost effectiveness of treatments should be expressed in terms of incremental cost per quality- adjusted life year. The time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and PSS perspective. The availability of any commercial arrangements for the intervention, comparator and	As per NICE scope	N/A

	Final scope issued by NICE	Decision problem addressed in the CS	EAG rationale if different from final NICE scope
	subsequent treatment technologies will be taken into account.		
CS, company submission; EAG, evidence assessment group; HINE-2, Hammersmith Infant Neurological Examination Module 2; HRQoL, Health-related quality of life; MFM, motor function measure; N/A, not applicable; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; PSS, Personal social service; SMA, spinal muscular atrophy; TA, technology appraisal			

2.2 *Population(s)*

There are two separate populations relevant to this MTA:

- People with types 0, 1, 2, 3 or 4 5q SMA
- People with pre-symptomatic 5q SMA confirmed with genetic testing with 1 to 4 SMN2 copies[4]

2.2.1 Relevant subgroups

If the evidence allows, the following subgroups will be considered:

- Number of SMN2 gene copies in people with pre-symptomatic SMA
- Functional status (non-sitter, sitter, walker)
- People who have had prior active treatment for SMA[4]

2.3 *Interventions*

2.3.1 Nusinersen

Nusinersen (Spinraza®; Biogen Idec) is an antisense oligonucleotide. It is intended to increase the production of survival motor neurone (SMN) protein, thereby helping to compensate for the defect in the SMN1 gene found in 5q spinal muscular atrophy. It has a marketing authorisation in the UK for "the treatment of 5q Spinal Muscular Atrophy".[14]

Nusinersen is administered by injection into the fluid filled space around the spinal cord (intrathecal injection).[15] A spinal anaesthesia needle is used for administration and sedation may be required. Ultrasound (or other imaging techniques) may be considered to guide administration.

In the marketing authorisation the dosage is 12mg (5 ml) per administration (on days 0, 14, 28 and 63 then every 4 months).[11]

NICE TA588 recommends treatment with Nusinersen as an option only as part of a managed access agreement for people who have either pre-symptomatic 5q SMA or type 1, 2 or 3 5q SMA.[11]

2.3.2 Risdiplam

Risdiplam (Evrysdi®, Roche Products Limited) is a survival motor neurone 2 (SMN2) pre-mRNA splicing modifier. It is intended to increase the production of SMN protein, thereby helping to compensate for the defect in the SMN1 gene found in 5q spinal muscular atrophy. It has a marketing authorisation in the UK for the treatment of 5q spinal muscular atrophy

(SMA) in patients with a clinical diagnosis of SMA Type 1, Type 2 or Type 3 or with one to four SMN2 copies.[12] Risdiplam is administered orally (via a syringe) once per day. It is supplied as a powder for oral solution and must be constituted by a healthcare professional prior to being dispensed. The recommended dose is determined by age and body weight (2 months to < 2 years of age=0.20 mg/kg; ≥ 2 years of age (< 20 kg) =0.25 mg/kg; ≥ 2 years of age (≥ 20 kg) =5 mg). A daily dose of above 5mg has not been studied.[16]

NICE TA755 recommends treatment with risdiplam as an option for treating 5q spinal muscular atrophy (SMA) in people of all ages with a clinical diagnosis of SMA types 1, 2 or 3 or with pre-symptomatic SMA and 1 to 4 SMN2 copies. It is recommended only if the conditions of a managed access agreement are followed.[12]

2.3.2.1 Place of nusinersen in the treatment/care pathway

For people with 5q SMA a possible place for nusinersen in the treatment pathway is as a monotherapy in addition to multidisciplinary supportive care.

At present, a Managed Access Agreement (MAA) is in place. Although the marketing authorisation for nusinersen includes all patients with 5q SMA, under the terms of the MAA it is used for pre-symptomatic people, and those with early onset (Type 1) or later onset (Type 2 and 3) SMA. This excludes severe infantile (Type 0) and adult-onset (Type 4) SMA. Within this agreement a pre-symptomatic person is defined as having the homozygous gene deletion or homozygous mutation, or compound heterozygous mutation detected in 5q SMA (including consideration of special warnings) and have 1-4 SMN2 copies. Pre-symptomatic persons are found by targeted testing of related individuals. Those for whom intrathecal injection is not technically feasible or is contraindicated are ineligible.[17]

2.3.2.2 Place of risdiplam in the treatment/care pathway

For people with pre-symptomatic SMA or SMA types 1, 2 or 3, a possible place for risdiplam in the treatment pathway is as a monotherapy in addition to multidisciplinary supportive care.[18]

At present an MAA is in place. Within this agreement patients must not have had successful treatment with onasemnogene abeparvovec or be on permanent ventilation. They must have a clinical diagnosis of SMA Types 1-3 or have been confirmed to have SMA via genetic testing and have 1-4 SMN2 copies.[18]

When NICE appraised risdiplam, nusinersen was the only disease modifying treatment available for SMA. Since then, NICE highly specialised technology appraisal guidance 15 recommends onasemnogene abeparvovec as an option for treating 5q spinal muscular atrophy with a bi-allelic mutation in the SMN1 gene and a clinical diagnosis of type 1 SMA in

babies, only if they are 6 months or younger, or they are aged 7 to 12 months, and their treatment is agreed by the national multidisciplinary team.[19] NICE highly specialised technology appraisal guidance 24 partially updated the guidance to also recommend onasemnogene abeparvovec for treating pre-symptomatic 5q spinal muscular atrophy (SMA) with a biallelic mutation in the SMN1 gene and up to 3 copies of the SMN2 gene in babies aged 12 months and under.[20] Onasemnogene abeparvovec is administered by intravenous infusion.[21]

It is possible that due to its oral administration, risdiplam would be a treatment option for people to whom nusinersen cannot be administered because an intrathecal injection is not feasible or contraindicated. The oral route of administration may also address possible issues related to nusinersen including the use of sedation, radiographic imaging and anxiety associated with lumbar puncture.

2.4 *Relevant comparator(s)*

Relevant comparators for this MTA based on the NICE scope are:

- Established clinical management.
- Best supportive care
- The interventions will be compared to each other.

In addition, for children aged 12 months and under with a bi-allelic mutation in the SMN1 gene and present with a clinical diagnosis of type 1 5q SMA or pre-symptomatically with up to 3 copies of the SMN2 gene.

- Onasemnogene abeparvovec

2.5 *Outcomes*

The outcomes to be addressed in this MTA based on the NICE scope are:

- motor function (including, where applicable, both age-appropriate gross motor milestones and fine motor skills)
- bulbar function (including, for example, swallowing and ability to communicate)
- frequency and duration of hospitalisation
- respiratory function
- complications of spinal muscular atrophy (including, for example, scoliosis and muscle contractures)
- need for non-invasive or invasive ventilation
- stamina and fatigue
- mortality
- adverse effects of treatment

- health-related quality of life (for patients and carers).

3 Methods for evidence synthesis of clinical effectiveness

A systematic literature review (SLR) of the evidence on the clinical effectiveness of nusinersen and risdiplam for treating 5q spinal muscular atrophy will be performed following the principles outlined in the Cochrane Handbook for Systematic Reviews of Interventions.[22] A flow diagram illustrating the number of records identified, included and excluded at each stage of the systematic literature review will be presented according to the PRISMA reporting guidelines.[23]

3.1 *Search strategy*

The search strategy will comprise the following main elements:

1) Searching of electronic bibliographic databases and other online sources,

2) Contacting experts in the field, and

3) Scrutiny of references of included studies and a selection of recent, relevant systematic reviews

4) Scrutiny of company submissions for any additional data.

A comprehensive search strategy will be developed by an information specialist in collaboration with the review team. Searches will be based around terms for spinal muscular atrophy, nusinersen and risdiplam and will use both free text keywords and, where available, thesaurus (MeSH/EMTREE) terms. Where possible, strategies to exclude animal studies, editorials/commentaries and similar publication types will be applied. Searches will be limited to studies published in English language, due to limited time and resources available for translation and to studies published since the dates of the company submissions for TA588 (nusinersen, original submission 1st October 2017)[10] and TA755 (risdiplam, literature search for company submission last updated in January 2020)[24] The search will initially be developed in Embase (via Ovid), and checked by a second information specialist not otherwise involved in the project before being translated for other sources. A draft Embase search strategy is provided in Appendix 10.2.

Searches will be conducted in a range of sources, including: Embase (Ovid); MEDLINE All (Ovid); Cochrane CENTRAL (Wiley); International HTA database (INAHTA); Science Citation Index and Conference Proceedings (Web of Science), ClinicalTrials.gov, WHO International Clinical Trials Registry Platform and websites of selected international HTA and

medicines approval agencies (NICE, Scottish Medicines Consortium, Canadian Agency for Drugs and Technologies in Health, Institute for Clinical and Economic Review). Records will be exported to EndNote 21, where duplicates will be systematically identified and removed.

3.2 *Study selection*

RCTs, and non-randomised trials, observational studies, case reports, SLRs and meta-analyses will be included in the SLR, and the evidence base for each intervention, types of 5q SMA and outcomes of relevance to the NICE final scope will be reported.

3.2.1 Inclusion criteria

Table 6 details the inclusion and exclusion criteria of the SLR. Based on these criteria, two reviewers will independently screen all titles and abstracts according to the inclusion criteria. Full texts of any titles/abstracts that may be relevant will be obtained where possible and the full text of each study will be assessed by two independent reviewers for inclusion in the SLR. Discrepancies will be resolved by discussion, with a third reviewer resolving any outstanding conflicts. Reasons for exclusion of full-text papers will be documented.

Table 6: Inclusion and exclusion criteria of the SLR

Factor	Inclusion criteria	Exclusion criteria
Design	RCTs, and non-randomised trials, observational studies, case reports, SLRs and meta-analyses [a]	Editorials Commentaries
Interventions	• Nusinersen monotherapy • Risdiplam monotherapy	• Concomitant or previous participation in any investigational drug • Any history of cell therapy
Population	People with types 0, 1, 2, 3 or 4 5q SMA, or pre-symptomatic 5q SMA confirmed with genetic testing with 1 to 4 SMN2 copies	• Received spinal fusion surgery following a diagnosis of scoliosis (prohibits safe administration of nusinersen) • Hospitalisation or respiratory conditions history or planned at the time of screening or tracheostomy. • History of surgery for scoliosis or hip fixation • Presence of clinically relevant ECG abnormalities before study drug administration • Unstable gastrointestinal, renal, hepatic, endocrine or

Factor	Inclusion criteria	Exclusion criteria
		cardiovascular system diseases
Comparators	• Established clinical management. • Best supportive care • The interventions will be compared to each other. In addition, for children aged 12 months and under with a bi-allelic mutation in the SMN1 gene and present with a clinical diagnosis of type 1 5q SMA or pre-symptomatically with up to 3 copies of the SMN2 gene. • Onasemnogene abeparvovec	• No exclusion criteria
Outcomes	The outcome measures to be considered include: • Motor function (including, where applicable, both age-appropriate gross motor milestones and fine motor skills) • Bulbar function (including, for example, swallowing and ability to communicate) • Frequency and duration of hospitalisation • Respiratory function • Complications of spinal muscular atrophy (including, for example, scoliosis and muscle contractures) • Need for non-invasive or invasive ventilation. • Stamina and fatigue • Mortality • Adverse effects of treatment • health-related quality of life (for patients and carers).	• No exclusion criteria
[a]SLRs and meta-analyses will be included past the abstract screening stage to enable bibliography searching but will be excluded at full-text stage. ECG, electrocardiogram; RCT: randomised controlled trial; SLR: systematic literature review		

3.2.2 Subgroups to be examined

The relevant subgroups for this appraisal are:

- Number of SMN2 gene copies in people with pre-symptomatic SMA

- Functional status (non-sitter, sitter, walker) and baseline motor function and level of motor function
- People who have had prior active treatment for SMA
- SMA type
- By age
- By prior treatment (naive or successful)
- Patients transition from childhood to adulthood

3.2.3 Outcomes to be examined

The list of the outcomes included in the NICE final scope and the variables to be extracted for these outcomes as part of the SLR are listed below:

- motor function (including, where applicable, both age-appropriate gross motor milestones and fine motor skills)
- bulbar function (including, for example, swallowing and the ability to communicate)
- frequency and duration of hospitalisation
- respiratory function
- complications of spinal muscular atrophy (including, for example, scoliosis and muscle contractures)
- need for non-invasive or invasive ventilation
- stamina and fatigue
- mortality
- adverse effects of treatment
- health-related quality of life (for patients and carers).

3.3 *Data extraction and quality appraisal*

3.3.1 Data extraction

For all included studies, the relevant data will be extracted independently by a single reviewer using a standardised data extraction form informed by the NHS Centre for Reviews and Dissemination (CRD).[25] Extracted data will be validated by a second reviewer and discrepancies will be resolved by discussion, with the involvement of a third reviewer when necessary. Where studies do not report summary statistics (e.g., mean score, standard deviation, standard error), we will attempt to calculate these parameters if individual participant data or related effect size-level statistics are provided. Where people with several types of 5q SMA are treated in one trial, we will extract information for relevant subtypes.

The extracted data will be entered into summary evidence tables (see Appendix 10.3). The extracted information will include:

- study characteristics (i.e., author's name, country, design, study setting, sample size in each arm, funding source, duration of follow-up(s), and methodological features corresponding to the Cochrane risk of bias assessment tool).
- patient baseline characteristics (i.e., trial inclusion/exclusion criteria; number of participants enrolled, and number of participants analysed; age, race, and gender; time from diagnosis of SMA to study entry; co-morbidities; prior active treatment; pre-symptomatic diagnosis; SMA type; number of SMN2 copies; relapse rate; age at symptom onset; age at treatment initiation; best motor function the person obtained).
- treatment characteristics (e.g., type of drug, method of administration, dose, and frequency; definition of best supportive care as described by trialists, treatment duration); and follow-up; switch between treatments.[26]
- outcome characteristics for each included outcome reported (e.g., definition of outcome measure; timing of measurement; scale of measurement; and effect size as presented, including mean difference, risk ratio, odds ratio, or hazard ratio, or arm-level data necessary to calculate an effect size). Measures of variability and statistical tests used will also be extracted (standard deviation, 95% CI, standard error, p-values).

3.3.2 Quality appraisal

Appraisal will be undertaken by two reviewers. Uncertainty and/or any disagreements will be crosschecked with a second reviewer and will be resolved by discussion. All primary studies will be appraised using the Cochrane risk of bias assessment tool.[27] A quality assessment will not be performed for single-arm non-randomised studies, which will be assumed to be at high risk of bias if they are used to inform relative treatment effects.

3.3.3 Patient and Public Involvement

We will document approaches used by the EAG to engage patient and public involvement (e.g., communities or clinicians) in our understanding of the condition and treatment pathway(s) and designing of the model-based economic analysis.

3.3.4 Protocol registration

3.4 *Methods of analysis/synthesis of clinical evidence*

3.4.1 Narrative synthesis

Data extracted from identified studies will be organised into tables which comprise essential information on the clinical aspects of the studies. These tables will include detailed design of the studies, interventions (Nusinersen and risdiplam) and comparators, population characteristics, and key outcome measures such as motor function, bulbar function hospitalisation frequency, respiratory function, complications of SMA, need for ventilation, stamina, fatigue, mortality, health-related quality of life, and adverse events. These will be presented as a comparison between the two (or more) treatment groups. A narrative synthesis will accompany each table, providing a comprehensive overview and critique of each study with special emphasis on the methodological quality and population diversity of the studies.

3.4.2 Feasibility assessment for indirect treatment comparison (ITC)

Key outcomes will be identified for potential including in ITC analyses.

If clinically appropriate, a naïve comparison of the treatments will be performed, with the limitations of the analysis clearly described. Depending on the available data, more advanced comparison might be feasible.

A propensity score-based comparison may be feasible (e.g. propensity score weighting (PSW) or matching-adjusted indirect comparison (MAIC)) if MAA or trial data are shared. If so, key variables for matching across populations will be identified through consultation with clinical experts. Estimated weightings will be assessed for suitability and the relative treatment effect estimated for the most relevant population.

Alternatively, network meta-analyses (NMA) may be most appropriate. If suitable data are available to perform a pair-wise meta-analysis between nusinersen and risdiplam, this will be done to test the effectiveness between the two treatments.

A thorough assessment of the quantity and quality of available data for each identified outcome will be conducted, also considering different subgroups such as number of SMN2 gene copies in people with pre-symptomatic SMA, functional status (non-sitter, sitter, walker), people who have had prior active treatment of SMA. Sources of data include published clinical trials and real-world evidence databases.

The transitivity assumption will be evaluated to ensure the appropriateness of the ITCs by comparing the similarity of factors such as disease severity, treatment history, eligibility criteria, treatment dosing, placebo response, endpoint definition and timing, and withdrawal frequency, among others.

Potential treatment effect modifiers (TEMs) will be identified which could include patient demographics, disease characteristics, or study design. A comparative analysis of distribution of the TEMs across the included studies will be conducted to ensure consistency.

3.4.3 Network meta-analysis

Statistical synthesis of the evidence will be performed if it is clinically appropriate and the number of studies permits this, i.e., if five or more relevant studies are identified and where it is meaningful to pool the data in ITCs. If a particular treatment, outcome, or studies cannot be included in statistical synthesis, a narrative synthesis will be provided. If non-comparative studies are identified, these will also be narratively summarised. Treatment effects will be presented as odds ratios (OR) for dichotomous data, weight mean differences for continuous data or hazard ratios (HR) as appropriate.

NMAs will be performed using a Bayesian Markov Chain Monte Carlo (MCMC) simulation with vague priors, using the NICE Decision Support Unit (DSU) Technical Support Document (TSD) 2 as a guide.[28] Both fixed (FE) and random effects (RE) model will be fitted with the best fitting model using measured of model fit such as the Deviance Information Criterion (DIC) or the Bayesian Information Criterion (BIC). Moreover, comparison will be made between prediction intervals from the FE and RE models. Statistical heterogeneity will be quantified using the between-study standard deviation (τ) and the I-squared statistic. The between-study standard deviation gives a direct measure of variance in the treatment effect across studies and larger values of τ indicates greater heterogeneity, and the I-squared statistic measures the proportion of variance across studies that is due to differences in population characteristics. Higher I-squared is indicative of higher levels of heterogeneity. If high heterogeneity is indicated in the chosen model, the feasibility of a network meta-regression model will be assessed which will be used to identify the characteristics of the study population that could explain this heterogeneity and identify subgroups of patients mostly likely to benefit from treatment.

Consistency between direct and indirect evidence will be assessed using a multifaced approach in the NMA. Node-splitting will be used to conduct examinations of specific treatment comparisons to ascertain the alignment of estimates derived from the sources being compared. Additionally, the design-by-treatment interaction model will be implemented to investigate potential variations in the interaction of TEMs in indirect and direct comparisons.

Global tests such as the Cochrane's Q or side-splitting analysis, and graphical approached such as comparison-adjusted Funnel plots will be used to provide an overarching

assessment of consistency throughout the network. Local tests will focus on specific closed loops, where they exist, to pinpoint potential inconsistencies in the network.

Analyses will be conducted in R version 4.2.3.

4 Methods for evidence synthesis of cost-effectiveness

In this health economic section, we will assess the cost-effectiveness of nusinersen and risdiplam for treating SMA. These interventions will be compared with:

- Established clinical management
- Best supportive care
- Each other (nusinersen compared to risdiplam).
- Onasemnogene aberparovvec (for children aged 12 months and under with a bi-allelic mutation in the SMN1 gene and present with a clinical diagnosis of type 1 5q SMA or pre-symptomatically with up to 3 copies of the SMN2 gene).

The main objective will be achieved through systematic identification of relevant economic evaluations, as well as reviewing the economic evidence provided by the companies.

4.1 *Search strategy*

The searches will comprise the following elements:

1) Searching of electronic bibliographic databases and other online sources
2) Contacting experts in the field, and
3) Scrutiny of references of studies included and a selection of recent, relevant systematic reviews.

A comprehensive search strategy will be developed by an information specialist in collaboration with the review team. Searches will be based around terms for spinal muscular atrophy, nusinersen, risdiplam and onasemnogene abeparvovec, with the addition of a validated search filter for economic evaluations where appropriate. The search will use both free text keywords and, where available, thesaurus (MeSH/EMTREE) terms. The search will initially be developed in Embase (via Ovid) and checked by a second information specialist not otherwise involved in the project before being translated for other sources. A draft Embase search strategy is provided in Appendix 10.5.

Searches will be conducted in a range of databases, including: Embase (Ovid); MEDLINE All (Ovid); International HTA database (INAHTA); Science Citation Index and Conference Proceedings (Web of Science), CEA Registry (Tufts Medical Center) and EconPapers

(RePec). Database searches will be supplemented with a targeted internet (Google) search and checking websites of selected international HTA and medicines approval agencies (NICE, Scottish Medicines Consortium, Canadian Agency for Drugs and Technologies in Health, Institute for Clinical and Economic Review, U.S. Food and Drug Administration, Medicines and Healthcare Products Regulatory Agency and European Medicines Agency).

Search results will be exported to EndNote 21, where duplicates will be systematically identified and removed.

4.1.1 Inclusion criteria

Reviewers will pilot a screening for based on a predefined inclusion criterion. Study selection will follow a 2-step process: screening of titles/abstracts and reading of full texts. Two reviewers will independently screen the titles and abstracts of the records identified through the searches, with potentially relevant titles/abstracts progressing to the full text stage. We will use the following inclusion criteria to screen all records identified:

- All types of economic evaluations (cost-effectiveness, cost-utility, cost-benefit, cost-consequence, or cost minimization analyses)
- Any healthcare setting, with the aim of being as inclusive as possible.
- The interventions or comparators as defined in Section 4
- The outcomes of the studies should be reported in terms of life-years gained (LYG) or quality-adjusted life years (QALYs).
- Only full publications in the English language will be considered, although relevant non-English studies will be mentioned.

The full text of all agreed abstracts will be read, of which those accepted by both reviewers will be included in the systematic review. Any disagreements between the reviewers will be resolved by discussion or by recourse to a third reviewer. The study flow and reasons for exclusion of full text articles will be documented using the preferred reporting items for systematic reviews and meta-analysis (PRISMA) flow diagram.[23]

4.2 *Data extraction and quality appraisal*

4.2.1 Data extraction

Information will be extracted from the relevant studies using an a *priori* pre-piloted data extraction sheet (*see* Appendix 10.6) based on items outlined by CHEERS 2022[29] and Wijnen et al.[30] Relevant information will be extracted on study details (e.g., title, author, and year of study), characteristics (e.g., population and age), treatment strategies (e.g.,

nusinersen, risdiplam, or onasemnogene abeparvovec), analytical methods (e.g., type of economic analysis, type of economic model, study perspective, resource use and costs and assumptions), results (e.g., base-case and sensitivity analysis results), discussion (e.g., study findings, comparison with other studies and limitations), and other (e.g., source of funding). If data are missing or has not been clearly reported efforts will be made to contact the corresponding author. A request for the missing information will be sent, allowing authors a two-week period to respond. If no response is received within this timeframe, it will be assumed that the requested data are not available.

Data extraction will be undertaken by one reviewer, then cross-checked by a second reviewer for accuracy. Any disagreements between the reviewers will be resolved by discussion or by recourse to a third reviewer.

4.2.2 Quality appraisal

All published economic evaluations included in this systematic review, along with any economic evaluations submitted to NICE by companies, will undergo a comprehensive appraisal. The reporting and methodological quality of each economic evaluation will be assessed using the consolidated health economic evaluation reporting standard (CHEERS) and appraised against the Philips' checklists, respectively. (see Appendix 10.7)[29, 31] The CHEERS checklist emphasises the study's relevance to policy and practice, as well as its transparency and reporting of results. The risk of bias/methodological quality will be assessed using the Philips' checklist, which comprises 57 items under two domains structure and data. Each economic analysis will be assessed by one reviewer and cross-checked by a second health economist. Any disagreements between the reviewers will be resolved by discussion or by recourse to a third reviewer.

4.3 *Synthesis of cost-effectiveness evidence*

Information extracted from the included studies will be summarised and presented in a tabular form. Due to the context-specific nature of economic evaluation, the conduct and findings of studies included in the systematic review will be summarised narratively. The results will be organised in texts and summary tables. We will highlight issues/concerns related to the applicability to a UK setting, outline the key drivers of cost-effectiveness, sources of uncertainty and provide a comprehensive overview of the cost-effectiveness evidence and discuss recommendations for the conduct of future economic modelling.

5 Economic modelling

If the available economic evidence is insufficient, we will develop a *de novo* economic model to assess the cost-effectiveness of nusinersen and risdiplam for the treatment of SMA. The structure of the model will be based on insights from the economic evaluations identified from the systematic review, TA588, TA755, HST24 and HST15,[11, 12, 19, 20] information provided by companies and clinical expert opinion. The economic model will require clinical and resource use and costs information related to nusinersen, risdiplam compared to BSC, onasemnogene abeparvovec (where applicable), established clinical management and each other. To populate the economic model, we will rely on the review of clinical effectiveness to gather the necessary clinical parameters. Additionally, we will gather estimates of health-related quality of life (HRQoL) or utility data from published literature. If the companies provide relevant unpublished HRQoL data, we will assess them for inclusion in the economic model. In cases where required parameters are not available from published studies or company submissions, we will consider expert clinical opinions.

Resource use information will be obtained from information provided by companies and valued using NHS reference costs,[32] Unit Costs of Health and Social Care,[33] eMit,[34] BNF,[35] and published sources. Costs will include both direct medical costs (e.g., drug costs, costs of adverse events, and monitoring and administering treatment) and direct non-medical costs (such as healthcare professional fees).

We will outline all assumptions made to have a workable model structure.

The economic analysis will be undertaken from the perspective of the NHS and personal social services (PSS). The deterministic base-case results of the analysis will be presented incrementally, in terms of an incremental cost-effectiveness ratio (ICER), expressed as cost per life-year gained (LYG) and cost per QALY gained. Cost-effectiveness will be assessed over a lifetime horizon, and all costs incurred, and benefits accrued will be discounted at 3.5% per annum after the first year in line with recommended guidelines,[36] and assuming that strategy is cost-effective at the £20,000-£30,000 per QALY. If appropriate, we will also consider analyses that considers severity modifiers.[36]

5.1 *Analysis of uncertainty*

A probabilistic model will be used with input parameters represented as probability distributions. Monte Carlo simulation will be utilized to incorporate uncertainty. Results of a probabilistic sensitivity analysis are reported in terms of incremental scatterplot and corresponding cost-effectiveness acceptability curves (CEACs).[37] Additionally, One-way sensitivity analysis will be conducted, and outputs will be presented in cost-effectiveness planes and acceptability curves. Uncertainty related to structural assumptions will be assessed through scenario analysis using alternative assumptions.

6 Handling of company submission(s)

The EAG will review and consider all data submitted by the company, provided it is received by the specified deadline. If the submitted data meet the criteria for inclusion in the review, they will be extracted and subjected to a quality assessment. In the case of economic evaluations included in the company's submission, their compliance with NICE's presentation guidelines will be examined. Furthermore, these evaluations will be evaluated based on their clinical validity, reasonableness of assumptions, and the appropriateness of the data used in the economic model. Should the EAG deem the existing economic evidence to be insufficiently robust, additional work will be conducted, either by adapting existing evidence or developing a new model.

Data designated as "commercial in confidence" in the company's submission and specified as confidential in the provided checklist will be distinctly marked in the assessment report. These data will be highlighted in blue, underlined, and accompanied by an indication of the relevant company name within brackets. Similarly, if any "depersonalized" data is extracted from a company submission and designated as confidential in the checklist, it will be emphasized in the assessment report. These data will be highlighted in pink, underlined, and presented accordingly.

7 Competing interest of authors

None of the authors have any competing interests.

8 Timetable/milestones

Draft Protocol sent to NICE	Tuesday 3 January 2024
Comment on draft Protocol sent to EAG	Tuesday 9 January 2024
Deadline for final Protocol from EAG	Tuesday 16 January 2024
Submissions sent to EAG	Thursday 25 April 2024
Progress report sent to NICE by NETSCC	Friday 10 May 2024
Draft Assessment Report (AR) due to NICE	Monday 20 May 2024
Final EAG report due to NICE	Tuesday 30 July 2024

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10 Appendices

10.1 *Comparison between original decision problems and the decision problem for this MTA*

Table 7: Original decision problems and the decision problem for this MTA

	Final scope issued by NICE for TA588	Decision problem addressed in CS (TA588)	Final scope issued by NICE for TA755	Decision problem addressed in CS (TA755)	Final scope issued by NICE for ID6195	Comparison of decision problems
Population	People with 5q SMA	Pre-symptomatic and symptomatic people with 5q SMA who have infantile onset (those who have or are most likely to develop type I) or later onset (those who have or are most likely to develop types II and III) SMA	People with spinal muscular atrophy	As per NICE scope	People with types 0, 1, 2, 3 or 4 5q SMA, or pre-symptomatic 5q SMA confirmed with genetic testing with 1 to 4 SMN2 copies	In line with populations outlined in previous scopes. However, in this MTA, SMA types are clearly stated.
Intervention	Nusinersen	Nusinersen	Risdiplam	As per NICE scope	• Nusinersen • Risdiplam Interventions are monotherapies in addition to existing clinical services and established clinical management	Includes both nusinersen and risdiplam
Comparator(s)	Best supportive care	Sham procedure and standard of care treatment	Best supportive care	As per NICE scope	• Established clinical management • Best supportive care • Each other	Includes other comparators compared

	Final scope issued by NICE for TA588	Decision problem addressed in CS (TA588)	Final scope issued by NICE for TA755	Decision problem addressed in CS (TA755)	Final scope issued by NICE for ID6195	Comparison of decision problems
					• Onasemnogene abeparvovec	
Outcomes	The outcome measures to be considered include: • Motor function (including, where applicable, age appropriate motor milestones) • Respiratory function • Complications of SMA • (including, for example, scoliosis • and muscle contractures) • Need for non-invasive or invasive ventilation • Stamina and fatigue • Mortality • Adverse effects of treatment • HRQoL	The outcome measures to be considered include: • Motor function (including, where applicable, age appropriate motor milestones) • Event-free survival (time to death or permanent assisted ventilation) and overall survival • Respiratory function • Need for non-invasive or • invasive ventilation • Mortality • Adverse effects of treatment • HRQoL	• Motor function (including, where applicable, age-appropriate motor milestones such as sitting, standing and walking) • Bulbar function (including, for example, swallowing and ability to communicate) • Frequency and duration of hospitalisation • Respiratory function • Complications of SMA (including, for example, scoliosis and muscle contractures)	The CS broadly aligns with the final scope issued by NICE. Not all outcomes listed in the final scope are, however, explicitly used in the economic models. Type 1 SMA: Health state occupancy in the economic model was based on motor milestone achievement using HINE-2, similarly to TA588. A separate health state for patients on permanent ventilation was included, as permanent ventilation is associated with additional costs and a more severe prognosis for patients with SMA type 1. Additional clinical outcomes from the	The outcome measures to be considered include: • Motor function (including, where applicable, both age-appropriate gross motor milestones and fine motor skills) • Bulbar function (including, for example, swallowing and ability to communicate) • Frequency and duration of hospitalisation • Respiratory function • Complications of spinal muscular atrophy (including, for example, scoliosis and muscle contractures)	Outcomes are largely in line with previous scopes, but more explicitly stated, and SMA types are more clearly stated

	Final scope issued by NICE for TA588	Decision problem addressed in CS (TA588)	Final scope issued by NICE for TA755	Decision problem addressed in CS (TA755)	Final scope issued by NICE for ID6195	Comparison of decision problems
			• Need for non-invasive or invasive ventilation • Stamina and fatigue • Mortality • Adverse effects of treatment • HRQoL	FIREFISH study will also be used to inform the economic model, such as event-free survival and respiratory outcomes. Type 2/3 SMA: Health state occupancy in the economic model was based on motor milestone achievement using MFM, the primary endpoint of the SUNFISH study. The MFM was selected as a primary endpoint on the basis that it can offer sufficient gradation in the assessment of functional abilities, to fully enable assessment of treatment efficacy in a broad population of Type 2 or 3 SMA patients, like the one included in SUNFISH.	• Need for non-invasive or invasive ventilation • Stamina and fatigue • Mortality • Adverse effects of treatment • HRQoL(for patients and carers).	

	Final scope issued by NICE for TA588	Decision problem addressed in CS (TA588)	Final scope issued by NICE for TA755	Decision problem addressed in CS (TA755)	Final scope issued by NICE for ID6195	Comparison of decision problems
				Additional clinical outcomes from the SUNFISH study will also be used to inform the economic model.		
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per QALY. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and personal social services perspective.	The economic analysis considers 2 de novo models to assess the cost-effectiveness of nusinersen using motor milestones health states – 1 relating to infantile onset SMA and the other to later onset SMA. The pre-symptomatic health state is being developed but could not be modelled in time for submission.	The cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and PSS perspective. The availability of any commercial arrangements for the intervention,	As per NICE scope	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial	As per previous decision problems but will consider commercial agreements and MAA.

	Final scope issued by NICE for TA588	Decision problem addressed in CS (TA588)	Final scope issued by NICE for TA755	Decision problem addressed in CS (TA755)	Final scope issued by NICE for ID6195	Comparison of decision problems
			comparator and subsequent treatment technologies will be taken into account.		arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. The availability of any managed access arrangement for the intervention will be taken into account.	
Subgroups to be considered	Consideration will be given to subgroups based on severity of disease (including considerations such as age of SMA onset, SMA type and genotype [including SMN2 copy number]). Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the	The pivotal trials in infantile onset (ENDEAR) and later onset SMA (CHERISH) included pre-specified subgroups based on disease duration and age at symptom onset. For infantile onset SMA patients the economic analysis has evaluated the subgroups based on age at onset of SMA symptoms and disease duration (>12 weeks and ≤12 weeks) from the ENDEAR trial	NR	NR	If the evidence allows the following subgroups will be considered: • Number of SMN2 gene copies in people with pre-symptomatic SMA • Functional status (non-sitter, sitter, walker) • People who have had prior active treatment for SMA	More subgroups will be included in the MTA if the evidence allows

	Final scope issued by NICE for TA588	Decision problem addressed in CS (TA588)	Final scope issued by NICE for TA755	Decision problem addressed in CS (TA755)	Final scope issued by NICE for ID6195	Comparison of decision problems
	marketing authorisation granted by the regulator.	For later onset SMA patients, subgroup analysis has not been conducted in the economic analysis due to the small subgroup sample sizes within				
Special considerations including issues related to equity or equality	NR	N/A	NR	NR	Guidance will only be issued in accordance with the marketing authorisations. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisations granted by the regulator.	
CS, company submission; HRQoL, health-related quality of life; MAA, Managed Access Agreement; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; N/A, not applicable; NR, not reported; PSS, Personal Social Services; SMA, spinal muscular atrophy; TA, technology appraisal;						

10.2 *Draft clinical effectiveness search strategy*

Embase (Ovid) 15/01/24

Embase Classic+Embase <1947 to 2024 Week 02>

1 exp hereditary spinal muscular atrophy/ or spinal muscular atrophy/ 14734

2 (((spinal or myelopathic) adj muscular atroph*) or spinal amyotroph* or SMA).kf,tw. 51326

3 (Werdnig adj Hoffman*).kf,tw.627

4 (Kugelberg adj Welander*).kf,tw. 353

5 1 or 2 or 3 or 4 [disease terms] 56788

6 nusinersen/ 1903

7 (nusinersen or spinraza*).kf,tn,tw. 1672

8 6 or 7 2062

9 risdiplam/ 558

10 (risdiplam or evrysdi*).kf,tn,tw. 442

11 9 or 10 611

12 5 and 8 1856

13 5 and 11 557

14 limit 12 to dc=20171001-20241231 1805

15 limit 13 to dc=20200101-20241231 494

16 (exp animal/ or exp animal experiment/) not (exp human/ or exp human experiment/ or conference abstract.pt.) 5864363

17 editorial.pt. 793149

18 14 or 15 1969

19 18 not (16 or 17) 1897

20 limit 19 to english language 1826

10.3 *Draft data extraction sheet*

Study details
Study ID (Endnote):
NCT number (Trials):
First author surname:
Year of publication:
Country:
Study design:
Study setting:
Duration of study:
Follow up period:
Sample size in each arm:
Funding:
Conflicts of interest stated:
Aim of the study
Participants
Trial inclusion criteria:
Trial exclusion criteria:
Subtypes:
Age:
Gender:
Race:
Total number of participants enrolled:
Sample attrition/drop out:
Number of participants analysed:
Lost to follow-up:
Reason for attrition/ lost to follow-up:

Time from diagnosis of SMA to study entry: Co-morbidities: Prior treatment: Pre-symptomatic diagnosis: SMA type: Number of SMN2 copies: Relapse rate: Age at symptom onset: Age at treatment initiation: Best motor function the person obtained:
Intervention and comparators (repeat if necessary for multiple intervention arms)
Type of drug: Method of administration: Dose: Frequency: Definition of best supportive care as described by trialists: Switch between treatments: Follow-up: Treatment duration:
Outcomes
Primary outcomes: Secondary outcomes: Method of assessing outcomes: Timing of assessment: Scale of measurement: Study end point: Adverse event: Health related quality of life: Yes/No; which measures used? Length of follow up:

Effect size: Statistical tests (standard deviation, 95% CI, standard error, p-values):
Comments

10.4 *Risk of bias assessment*

Study identification Include author, title, reference, year of publication					
Guideline topic:	Review question no:				
Checklist completed by:					
		Circle or highlight one option for each question			
A. Selection bias (systematic differences between the comparison groups)					
A1	An appropriate method of randomisation was used to allocate participants to treatment groups (which would have balanced any confounding factors equally across groups)	Yes	No	Unclear	N/A
A2	There was adequate concealment of allocation (such that investigators, clinicians and participants cannot influence enrolment or treatment allocation)	Yes	No	Unclear	N/A
A3	The groups were comparable at baseline, including all major confounding and prognostic factors	Yes	No	Unclear	N/A
Based on your answers to the above, in your opinion was selection bias present? If so, what is the likely direction of its effect?					
Low risk of bias Unclear/unknown risk High risk of bias					

Likely direction of effect:					
B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)					
B1	The comparison groups received the same care apart from the intervention(s) studied	Yes	No	Unclear	N/A
B2	Participants receiving care were kept 'blind' to treatment allocation	Yes	No	Unclear	N/A
B3	Individuals administering care were kept 'blind' to treatment allocation	Yes	No	Unclear	N/A
Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?					
Low risk of bias Unclear/unknown risk High risk of bias					
Likely direction of effect:					
C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)					
C1	All groups were followed up for an equal length of time (or analysis was adjusted to allow for differences in length of follow-up)	Yes	No	Unclear	N/A
C2	a. How many participants did not complete treatment in each group?				
	b. The groups were comparable for treatment completion (that is, there were no important or systematic differences between groups in terms of those who did not complete treatment)	Yes	No	Unclear	N/A
C3	a. For how many participants in each group were no outcome data available? .				
	b. The groups were comparable with respect to the availability of outcome data (that is, there were no important or systematic differences between groups in terms of those for whom outcome data were not available).	Yes	No	Unclear	N/A
Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?					
Low risk of bias Unclear/unknown risk/High risk of bias					
Likely direction of effect:					
D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)					
D1	The study had an appropriate length of follow-up	Yes	No	Unclear	N/A
D2	The study used a precise definition of outcome	Yes	No	Unclear	N/A
D3	A valid and reliable method was used to determine the outcome	Yes	No	Unclear	N/A

D4	Investigators were kept 'blind' to participants' exposure to the intervention	Yes	No	Unclear	N/A
D5	Investigators were kept 'blind' to other important confounding and prognostic factors	Yes	No	Unclear	N/A
Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?					
Low risk of bias Unclear/unknown risk High risk of bias					
Likely direction of effect:					

10.5 *Draft cost-effectiveness search strategy*

Embase (Ovid); 15/01/24

Embase Classic+Embase <1947 to 2024 Week 02>

1 exp hereditary spinal muscular atrophy/ or spinal muscular atrophy/ 14734

2 (((spinal or myelopathic) adj muscular atroph*) or spinal amyotroph* or SMA).kf,tw. 51326

3 (Werdnig adj Hoffman*).kf,tw.627

4 (Kugelberg adj Welander*).kf,tw. 353

5 1 or 2 or 3 or 4 [disease terms] 56788

6 nusinersen/ 1903

7 (nusinersen or spinraza*).kf,tn,tw. 1672

8 risdiplam/ 558

9 (risdiplam or evrysdi*).kf,tn,tw. 442

10 onasemnogene abeparvovec/ 913

11 (onasemnogene or zolgensma*).kf,tn,tw. 749

12 6 or 7 or 8 or 9 or 10 or 11 2804

13 Economics/ 248128

14 Cost/ 67351

15 exp Health Economics/ 1073335

16 Budget/ 34646

17 budget*.ti,ab,kw. 49430

18 (economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ti,kw. 329048

19 (economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ab. /freq=2 557486

20 (cost* adj2 (effective* or utilit* or benefit* or minimi* or analy* or outcome or outcomes)).ab,kw. 294738

21 (value adj2 (money or monetary)).ti,ab,kw. 4250

22 Statistical Model/ 176338

23 economic model*.ab,kw. 6427

24 Probability/ 153608

25 markov.ti,ab,kw. 37791

26 monte carlo method/ 52466

27 monte carlo.ti,ab,kw. 63586

28 Decision Theory/ 1898

29 Decision Tree/23126

30 (decision* adj2 (tree* or analy* or model*)).ti,ab,kw. 53924

31 or/13-30 [Economic Evaluations & Models - Embase. In: CADTH Search Filters Database. Ottawa: CADTH; 2023: https://searchfilters.cadth.ca/link/15] 2084621

32 socioeconomics/ 171933

33 exp Quality of Life/ 674566

34 quality of life.ti,kw. 178573

35 ((instrument or instruments) adj3 quality of life).ab. 5509

36 Quality-Adjusted Life Year/ 36408

37 quality adjusted life.ti,ab,kw. 27189

38 (qaly* or qald* or qale* or qtime* or life year or life years).ti,ab,kw. 46024

39 disability adjusted life.ti,ab,kw. 6804

40 daly*.ti,ab,kw. 6710

41 (sf36 or sf 36 or short form 36 or shortform 36 or short form36 or shortform36 or sf thirtysix or sfthirtysix or sfthirty six or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).ti,ab,kw. 51089

42 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six or shortform6 or short form6).ti,ab,kw. 3056

43 (sf8 or sf 8 or sf eight or sfeight or shortform 8 or shortform 8 or shortform8 or short form8 or shortform eight or short form eight).ti,ab,kw. 1052

44 (sf12 or sf 12 or short form 12 or shortform 12 or short form12 or shortform12 or sf twelve or sftwelve or shortform twelve or short form twelve).ti,ab,kw. 12637

45 (sf16 or sf 16 or short form 16 or shortform 16 or short form16 or shortform16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).ti,ab,kw. 73

46 (sf20 or sf 20 or short form 20 or shortform 20 or short form20 or shortform20 or sf twenty or sftwenty or shortform twenty or short form twenty).ti,ab,kw. 619

47 (hql or hqol or h qol or hrqol or hr qol).ti,ab,kw. 40485

48 (hye or hyes).ti,ab,kw.188

49 (health* adj2 year* adj2 equivalent*).ti,ab,kw. 53

50 (pqol or qls).ti,ab,kw. 764

51 (quality of wellbeing or quality of well being or index of wellbeing or index of well being or qwb).ti,ab,kw. 618

52 nottingham health profile*.ti,ab,kw. 1685

53 nottingham health profile/ 667

54 sickness impact profile.ti,ab,kw. 1296

55 sickness impact profile/ 2402

56 health status indicator/ 3544

57 (health adj3 (utilit* or status)).ti,ab,kw. 122295

58 (utilit* adj3 (valu* or measur* or health or life or estimat* or elicit* or disease or score* or weight)).ti,ab,kw. 26331

59 (preference* adj3 (valu* or measur* or health or life or estimat* or elicit* or disease or score* or instrument or instruments)).ti,ab,kw. 19807

60 disutilit*.ti,ab,kw. 1316

61 rosser.ti,ab,kw. 144

62 willingness to pay.ti,ab,kw. 13630

63 standard gamble*.ti,ab,kw. 1225

64 (time trade off or time tradeoff).ti,ab,kw. 2446

65 tto.ti,ab,kw. 2311

66 (hui or hui1 or hui2 or hui3).ti,ab,kw. 3242

67 (eq or euroqol or euro qol or eq5d or eq 5d or euroqual or euro qual).ti,ab,kw. 39946

68 duke health profile.ti,ab,kw. 121

69 functional status questionnaire.ti,ab,kw. 178

70 dartmouth coop functional health assessment*.ti,ab,kw. 14

71 or/32-70 [Economic - Health Utilities / Quality of Life - Standard - Embase. In: CADTH Search Filters Database. Ottawa: CADTH; 2022: https://searchfilters.cadth.ca/link/18.] 1031404

72 5 and 12 and 31 385

73 5 and 12 and 71 231

74 72 or 73 507

10.6 *Draft data extraction sheet*

Date:

Study ID:

Name of first reviewer:

Name of second reviewer:

Study details	
Study title	
First author	
Co-authors	
Source of publication Journal yy;vol(issue):pp	
Publication link	
Language	
Publication type	
Inclusion criteria/study eligibility/PICOS	
Population	
Intervention(s)	
Comparator(s)	
Outcome(s)	
Study design	
Methods	
Target population and subgroups	
Setting and location	
Approach to engagement with patients and others affected by the study	
Study perspective	
Comparators	
Time horizon	
Discount rate	
Outcome(s)	
Measurement of effectiveness	
Measurement and valuation of preference-based outcomes	
Methods for identifying resource use	
Resource use and costs	
Data source of resource use	

Currency, price date and conversion	
Analytic approach and model type (if applicable)	
Assumptions	
Results	
Study parameters	
Incremental costs and outcomes	
Characterising uncertainty	
Discussion	
Study findings	
Limitations	
Generalisability	
Other	
Source of funding	
Conflicts of interest	
Comments	
Authors conclusion	
Reviewer's conclusion	

10.7 *Quality assessment*

Critical appraisal of the economic evaluation studies using the CHEERS checklist (adapted from Husereau et al., 2022).[29]

CHEERS criteria	**Study and location where item is reported**			
	Study 1	**Study 2**	**Study 3**	**Study 4**
Title				
1 **Title**: Identify the study as an economic evaluation and specify the interventions being compared				
Abstract				
2 **Abstract**: Provide a structured summary that highlights context, key methods, results, and alternative analyses.				
Introduction				
3 **Background & objectives**: Give the context for the study, the study question, and its practical relevance for decision making in policy or practice.				
Methods				

CHEERS criteria	Study and location where item is reported			
	Study 1	Study 2	Study 3	Study 4
4 **Health economic analysis plan**: Indicate whether a health economic analysis plan was developed and where available.				
5 **Study population**: Describe characteristics of the study population (such as age range, demographics, socioeconomic, or clinical characteristics).				
6 **Setting and Location**: Provide relevant contextual information that may influence findings.				
7 **Comparators**: Describe the interventions or strategies being compared and why chosen.				
8 **Perspective**: State the perspective(s) adopted by the study and why chosen.				
9 **Time Horizon**: State the time horizon for the study and why appropriate.				
10 **Discount Rate**: Report the discount rate(s) and reason chosen.				
11 **Selection of outcomes**: Describe what outcomes were used as the measure(s) of benefit(s) and harm(s).				
12 **Measurement of outcomes**: Describe how outcomes used to capture benefit(s) and harm(s) were measured.				
13 **Valuation of outcomes**: Describe the population and methods used to measure and value outcomes.				
14 **Measurement and valuation of resources and costs**: Describe how costs were valued.				
15 **Currency, price date, and conversion**: Report the dates of the estimated resource quantities and unit costs, plus the currency and year of conversion.				
16 **Rationale and description of model**: If modelling is used, describe in detail, and why used. Report if the model is publicly available and where it can be accessed.				
17 **Analytics and assumptions**: Describe any methods for analysing or statistically transforming data, any extrapolation methods, and approaches for validating any model used.				
18 **Characterizing heterogeneity**: Describe any methods used for estimating how the results of the study vary for subgroups.				
19 **Characterizing distributional effects**: Describe how impacts are distributed across different individuals or adjustments made to reflect priority populations.				
20 **Characterizing uncertainty**: Describe methods to characterise any sources of uncertainty in the analysis.				
21 **Approach to engagement with patients and others affected by the study**: Describe any approaches to engage patients or service recipients, the general public, communities, or				

CHEERS criteria	Study and location where item is reported			
	Study 1	Study 2	Study 3	Study 4
stakeholders (such as clinicians or payers) in the design of the study.				
Results				
22 **Study parameters**: Report all analytic inputs (such as values, ranges, references) including uncertainty or distributional assumptions.				
23 **Summary of main results**: Report the mean values for the main categories of costs and outcomes of interest and summarise them in the most appropriate overall measure.				
24 **Effect of uncertainty**: Describe how uncertainty about analytic judgments, inputs, or projections affect findings. Report the effect of choice of discount rate and time horizon, if applicable.				
25 **Effect of engagement with patients and others affected by the study**: Report on any difference patient/service recipient, general public, community, or stakeholder involvement made to the approach or findings of the study				
Discussion				
26 **Study findings, limitations, generalizability, and current knowledge**: Report key findings, limitations, ethical or equity considerations not captured, and how these could affect patients, policy, or practice.				
Other				
27 **Source of Funding**: Describe how the study was funded and any role of the funder in the identification, design, conduct, and reporting of the analysis				
28 **Conflicts of Interest**: Report authors conflicts of interest according to journal or International Committee of Medical Journal Editors requirements.				

"Reported": If information reported.
"Not reported": If information is otherwise not reported.
"Not applicable": If an item does not apply to a particular economic evaluation.

Critical appraisal of the economic models using an adapted Philips checklist (Philips et al., 2004).[31]

Philips criteria		Response	Comments
STRUCTURE			
1	Is there a clear statement of the decision problem?		
2	Is the objective of the model specified and consistent with the stated decision problem?		
3	Is the primary decision maker specified?		
4	Is the perspective of the model stated clearly?		
5	Are the model inputs consistent with the stated perspective?		
6	Has the scope of the model been stated and justified?		
7	Are the outcomes of the model consistent with the perspective, scope and overall objective of the model?		
8	Is the structure of the model consistent with a coherent theory of the health condition under evaluation?		
9	Are the sources of the data used to develop the structure of the model specified?		
10	Are the causal relationships described by the model structure justified appropriately?		
11	Are the structural assumptions transparent and justified?		
12	Are the structural assumptions reasonable given the overall objective, perspective and scope of the model?		
13	Is there a clear definition of the options under evaluation?		
14	Have all feasible and practical options been evaluated?		
15	Is there justification for the exclusion of feasible options?		
16	Is the chosen model type appropriate given the decision problem and specified casual relationships within the model?		
17	Is the time horizon of the model sufficient to reflect all important differences between the options?		
18	Are the time horizon of the model, the duration of treatment and the duration of treatment described and justified?		
19	Do the disease states (state transition model) or the pathways (decision tree model) reflect the underlying biological process of the disease in question and the impact of interventions?		
20	Is the cycle length defined and justified in terms of the natural history of disease?		
DATA			
21	Are the data identification methods transparent and appropriate given the objectives of the model?		
22	Where choices have been made between data sources are these justified appropriately?		

Philips criteria		Response	Comments
23	Has particular attention been paid to identifying data for the important parameters of the model?		
24	Has the quality of the data been assessed appropriately?		
25	Where expert opinion has been used are the methods described and justified?		
26	Is the data modelling methodology based on justifiable statistical and epidemiological techniques?		
27	Is the choice of baseline data described and justified?		
28	Are transition probabilities calculated appropriately?		
29	Has a half-cycle correction been applied to both costs and outcomes?		
30	If not, has the omission been justified?		
31	If relative treatment effects have been derived from trial data, have they been synthesised using appropriate techniques?		
32	Have the methods and assumptions used to extrapolate short-term results to final outcomes been documented and justified?		
33	Have alternative extrapolation assumptions been explored through sensitivity analysis?		
34	Have assumptions regarding the continuing effect of treatment once treatment is complete been documented and justified?		
35	Have alternative assumptions regarding the continuing effect of treatment been explored through sensitivity analysis		
36	Are the costs incorporated into the model justified?		
37	Has the source for all costs been described?		
38	Have discount rates been described and justified given the target decision maker?		
39	Are the utilities incorporated into the model appropriate?		
40	Is the source of utility weights referenced?		
41	Are the methods of derivation for the utility weights justified?		
42	Have all data incorporated into the model been described and referenced in sufficient detail?		
43	Has the use of mutually inconsistent data been justified (i.e. are assumptions and choices appropriate?)		
44	Is the process of data incorporation transparent?		
45	If data have been incorporated as distributions, has the choice of distributions for each parameter been described and justified?		
46	If data have been incorporated as distributions, is it clear that second order uncertainty is reflected?		
47	Have the four principal types of uncertainty been addressed?		
48	If not, has the omission of particular forms of uncertainty been justified?		

Philips criteria		Response	Comments
49	Have methodological uncertainties been addressed by running alternative versions of the model with different methodological assumptions?		
50	Is there evidence that structural uncertainties have been addressed via sensitivity analysis?		
51	Has heterogeneity been dealt with by running the model separately for different sub-groups?		
52	Are the methods of assessment of parameter uncertainty appropriate?		
53	If data are incorporated as point estimates, are the ranges used for sensitivity analysis stated clearly and justified?		
54	Is there evidence that the mathematical logic of the model has been tested thoroughly before use?		
55	Are any counterintuitive results from the model explained and justified?		
56	If the model has been calibrated against independent data, have any differences been explained and justified?		
57	Have the results been compared with those of previous models and any differences in results explained?		
N- No; N/A- Not Applicable; Y- Yes; UNC-Unclear			