EUnetHTA Joint Action 3 WP5 Strand B:

Post-launch evidence generation (PLEG) and registries

EUnetHTA WP5B PLEG Pilot on Nusinersen (Spinraza®)

Common Evidence Gaps report

April 2020

This document is part of the project / joint action '724130 / EUnetHTA JA3' which has received funding from the European Union's Health Programme (2014-2020).

DOCUMENT HISTORY AND CONTRIBUTORS

Version number	Date	Description
V1	28/11/2018	1st draft
V2	31/05/2019	2nd draft addressing comments from pilot team members
V3	07/04/2020	3rd draft updating the information on HTA assessment status and reimbursement; addressing additional comments from pilot team members
V4	20/04/2020	Medical editing

Pilot team

Responsibility/role	HTA Body/affiliation	Team member name
Pilot lead and coordination	Italian Medicines Agency (AIFA)	Agnese Cangini
Pilot members	Norwegian Medicines Agency (NOMA)	Einar Andreassen, Krystina Hviding
	Ministry of Health Croatia	Mirjana Huic, Romana Tandara Haček
	Finnish Medicines Agency (FIMEA)	Hanna-Mari Jauhonen, Piia Rannanheimo
	National Health Care Institute of the Netherlands (ZIN)	Krista Schutte
	Portuguese National Authority of Medicines and Health Products (INFARMED)	Jorge Rodrigues, Claudia Santos, Mariane Cossito

Further contributors

Responsibility/role	HTA Body/affiliation	Name
WP5B project management; internal review	Haute Autorité de santé (HAS) / HTA international unit (WP5B coordinator)	Irena Guzina
Medical editing [v3]	Compuscript	Moira Keaney

Conflict of interest

All participants involved in the production of this pilot have declared they have no conflicts of interest in relation to the technology assessed according to the EUnetHTA declaration of interest and confidentiality undertaking form.

Stakeholder involvement

The company in charge of the development of the product has been contacted at the beginning of the pilot and kept informed about different pilot steps and outputs. No other stakeholders have been involved on pilot level at the stage of the production of this report.

How to cite this document
Please cite this document as follows:

EUnetHTA PLEG_FP_01. Pilot Team. PLEG pilot on Nusinersen (Spinraza). Common Evidence Gaps report. Diemen (The Netherlands): EUnetHTA; 2020. [Date of citation]. Report No.: PLEG_FP_01. Available from: https://www.eunethta.eu

TABLE OF CONTENTS

List of abbreviations 5
1 Background 6
1.1 Aim and rationale of the pilot 6
1.2 Overview of the disease or health condition 7
Spinal muscular atrophy (SMA) 7
1.3 Nusinersen (Spinraza®): main characteristics 7
Regulatory status of Spinraza® 8
HTA status of Spinraza® 8
Reimbursement status of Spinraza® 8
2 Main assessment results and common evidence gaps from national HTAs 10
2.1 Main body of evidence assessed in the national HTAs 10
2.2 Assessment results and common evidence gaps 10
2.3 Common research recommendations 13
APPENDIX 1. Clinical classification of spinal muscular atrophy (SMA) 16
APPENDIX 2. Questionnaire on evidence gaps template 17
Sources 19

List of abbreviations

AIFA	Agenzia Italiana del Farmaco
CHOP INTEND	Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders
CI	Confidence interval
EPAR	European Public Assessment Report
EUnetHTA	European Network for Health Technology Assessment
FIMEA	Finnish Medicines Agency
HAS	Haute Autorité de Santé
HFMSE	Hammersmith Functional Motor Scale–Expanded
HINE	Hammersmith Infant Neurological Examination
HR	Hazard ratio
HTA	Health Technology Assessment
INFARMED	Portuguese National Authority of Medicines and Health Products
NOMA	Norwegian Medicines Agency
PLEG	Post-launch evidence generation
RWD	Real world data
SMA	Spinal muscular atrophy
WHO	World Health Organization
ZIN	Zorginstituut Nederland

1 BACKGROUND

1.1 Aim and rationale of the pilot

This pilot was conducted within EUnetHTA Joint Action 3 Work Package 5, for which the aim is to help in generating optimal and robust evidence for health technologies (pharmaceuticals or others) throughout the technology lifecycle, bringing benefits for patient access and public health.

Work Package 5 consists of two strands: strand A focuses on initial evidence generation and the activity of Early Dialogues, while strand B focuses on Post-Launch Evidence Generation. More information on the specific WP5B activities can be found at https://eunethta.eu/pleg/.

This document is an output of a WP5B PLEG product-specific pilot on Spinraza®. The main WP5B pilot steps are presented in Figure 1.

This pilot was proposed by the Italian Medicines Agency (AIFA) considering the uncertainties noted during the national HTA. The proposal was supported by the following considerations:

- The collection of data such as patient numbers and characteristics, treatment duration and main outcome measures will greatly support the decision-making process for pricing and reimbursement and for subsequent reassessments.
- In the setting of a rare disease, collaboration among member states in the definition of a minimum data set and in gathering evidence coming from different registries and databases is crucial for HTA purposes.

The main objectives of this pilot are therefore as follows:

- To build a common and agreed data set for collection (which will serve as a basis for common analysis afterwards);
- To gather locally generated data (when possible) from different sources (databases, registries, health care records); and
- To assess possible levels of cross-border collaboration on the generation and exchange of real world data (RWD).

The present report corresponds to step 4 of the pilot, and its aim is to synthesise the main evidence gaps and research needs identified by pilot team members in their national HTA (performed at different time points after centralised marketing authorisation approval).

This work will form the basis for the next step of the pilot (step 5) which will consist of agreeing on the common data set for RWD collection for this drug. This common data set will reflect the basis of RWD collection individually set up on a national level by pilot team members.

The final report (step 6) will possibly include RWD from different sources; however, its main goal is to present common data, lessons and issues of any kind related to international collaborations on RWD. This will be key information to pave the way towards effective future collaborations on PLEG.

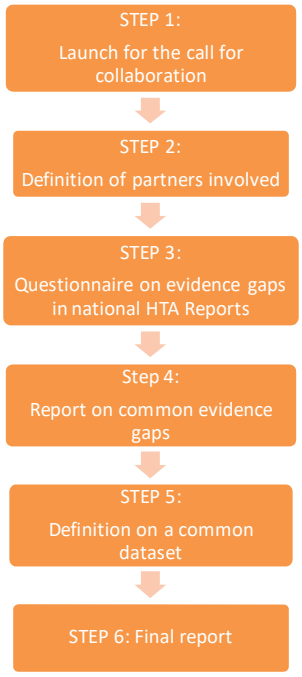

Figure 1. Main steps of the pilot.

1.2 Overview of the disease or health condition

Spinal muscular atrophy (SMA)

SMA is an autosomal recessive neuromuscular serious, debilitating, and life-threatening rare disease, with a global incidence of 8.5 to 10.3 per 100,000 live births characterized by degeneration of the motor neurons in the anterior horn of the spinal cord, resulting in atrophy of the voluntary muscles of the limbs and trunk. SMA is the most common genetic disorder linked to infant death worldwide.[1]

SMA has been categorised into types 0, I, II, III and IV, ranging in severity from babies who are born with severe impairment and die within weeks of birth (type 0) to disease that manifests in adult life with proximal muscle weakness (type IV). The most common variants (types I, II and III) all present with a presymptomatic period and can be classified prospectively according to the age of symptom onset and *SMN2* gene copy number as infantile-onset and later-onset. A detailed description of SMA types is provided in Appendix 1.

1.3 Nusinersen (Spinraza®): main characteristics

At the time of launch of this pilot, with the exception of Nusinersen (Spinraza®), there were no therapies approved in Europe for the treatment of SMA and medical care was only supportive, focused on respiratory support, nutritional support, and management of resulting musculotendinous contractures and neuromuscular scoliosis via bracing, physical therapy and surgery.[2] Therefore, a significant unmet clinical need exists for these patients.

Spinraza® is an antisense oligonucleotide that represents the first disease-modifying agent in SMA. Spinraza® increases levels of SMN2 protein and therefore improves motor function.

[1] Assessment report. www.ema.europa.eu/en/documents/assessment-report/spinraza-epar-public-assessment-report_en.pdf

[2] January 2020 update: the US Food and Drug Administration has authorized Zolgensma®, a gene therapy, for the treatment of pediatric patients aged <2 years with spinal muscular atrophy (SMA) with biallelic mutations in the survival motor neuron 1 (*SMN1*) gene (the first registration in Europe is expected to follow).

Regulatory status of Spinraza®

Spinraza® which has received an orphan designation in 2012 obtained the EU Marketing Authorisation in May 2017 for the treatment of 5q Spinal Muscular Atrophy. To address uncertainties that emerged during the review by the Committee for Medicinal Products for Human Use,[3] the company has to conduct two post-authorisation efficacy studies (SHINE, NCT02594124; and NURTURE, NCT02386553). The company will have to put in place a risk management pan comprising various measures, including a collaboration with existing disease registries that will collect Nusinersen treatment information.

HTA status of Spinraza®

Table 1 presents the HTA status of pilot team members.

Table 1. HTA status among pilot team members

HTA body	HTA status	Date of assessment finalisation
AIFA (IT)	Finalised	27.9.2017 (publication of P&R decision on Official Gazette)
AAZ (CR)	Finalised	17.01.2019 (HTA report finalised but not publicly available)
FIMEA (FI)	Finalised	19.09.2017 (HTA report published)
INFARMED (PT)	Finalised	20.12.2018 (HTA report published)
NOMA (NO)	Finalised	09.10.2017 (HTA report published)
ZIN (NL)	Finalised	05.02.2018 (HTA report published)

Updated in May 2019.

Reimbursement status of Spinraza®

Table 2 shows the reimbursement status by country for the pilot team.

Table 2. Reimbursement status across countries

Country	Reimbursement status	Decision date
Italy	Reimbursement for SMA types I, II and III	25 Sept 2017
Croatia	For the treatment of SMA caused by mutation on chromosome 5q with a minimum of two copies of the *SMN2* gene. The first impact assessment is performed after 6 months and then every 4 months before the next dose of the drug is administered. **Patients with SMA type I who do not require mechanical ventilation** *Discontinuation criteria* Permanent mechanical ventilation (for >16 h/day for 21 days continuously). If disease progression occurs despite treatment, a new decision to continue Nusinersen therapy should be made after 4 months using the same criteria as when starting therapy. **Patients with SMA type II aged <18 years who do not require mechanical ventilation** If disease progression occurs despite Nusinersen treatment, a new decision to continue therapy should be made after 4 months. There should be no deterioration of motor function measured using the HFMSE and continued respiratory function is mandatory. **Patients with SMA type III aged <18 years** The criteria for discontinuation of therapy are the same as for patients with SMA type III. Drug administration only at the Reference Centre of the Ministry of Health for Paediatric Neuromuscular Diseases at the Clinical Hospital Centre Zagreb. The treatment is approved by the Hospital Drugs Committee on recommendation of a neurologist paediatrician with the prior consent of the National Committee for the initiation and continuation of Nusinersen treatment. Treatment is approved for particularly expensive drugs.	May 2018

[3] From the assessment report: "The imposed post-authorization measures are aimed, among other things, at gathering sufficient data to enable future decisions about the necessity of dose adjustment." … "The evidence for maintenance of efficacy in the long term was not available as a part of this submission and post-authorization measures have been requested to address this." www.ema.europa.eu/en/documents/assessment-report/spinraza-epar-public-assessment-report_en.pdf

Country	Reimbursement status	Decision date
Finland	National recommendation restricted to a particular population: Nusinersen may be used for the treatment of SMA when: - SMA diagnosis is before the age of 2 years and the onset of clinical signs and symptoms is before the age of 20 months - Treatment initiation is before the age of 17 years - The patient does not need permanent invasive ventilation -There is no other medical contraindication to Nusinersen treatment This recommendation is conditional on a substantial reduction in price	15 Mar 2018
Portugal	Reimbursement for SMA types I, II and III	20 Dec 2018
Norway	Reimbursement restricted to a particular population: Nusinersen (Spinraza®) may be used for treatment of children with SMA according to the following prerequisites: **SMA type I** Not SMA type 0 (excluded from treatment with Spinraza®) Patients are expected to have oxygen saturation >95 % without any extra oxygen or ventilation assistance, including continuous positive airway pressure Patients should have a minimum of 2 copies of the *SMN2* gene **SMA type II** Patients are not dependent on artificial ventilation or extra oxygen to achieve oxygen saturation of >95% Patients should have a minimum of 2 copies of the *SMN2* gene **SMA type III** Children diagnosed with SMA type III and with confirmed onset of symptoms before 3 years of age (type IIIa) will be considered for treatment according to the same criteria as for children with SMA type II. In addition to selection criteria, there are established criteria for treatment cessation Results are evaluated at 12 months after initiation of treatment with Spinraza® and then every 4th month. Children will be treated at main regional hospitals with clinical expertise in SMA.	22 Oct 2018
The Netherlands	Reimbursement granted for three SMA subgroups: - SMA with infantile-onset (symptom onset before 6 months of age) with a disease duration of <26 weeks at the start of treatment - SMA with later childhood-onset (symptom onset at 6–20 months of age) in children with a disease duration of <94 months at the start of treatment - Presymptomatic infants with a genetic diagnosis of 5q SMA and with 2 or 3 *SMN2* copies	August 2018

Updated in February 2019.

Abbreviations: HFMSE=Hammersmith Functional Motor Scale-Expanded; SMA=spinal muscular atrophy.

2 MAIN ASSESSMENT RESULTS AND COMMON EVIDENCE GAPS FROM NATIONAL HTAS

A questionnaire (Appendix 2) to collect evidence gaps and research needs identified by the pilot team members in their national HTA was elaborated by AIFA on the basis of the EUnetHTA position paper on how to best formulate research recommendations for primary research arising from HTA. The questionnaire was filled out by the pilot team members. The questionnaire comprised two main sections:

1. Assessment results; and
2. Recommendations for research.

On the basis of the responses received, the pilot team identified and highlighted commonalities, which are presented in the Sections 2.1–2.3.

2.1 Main body of evidence assessed in the national HTAs

1) Pivotal study CS3B (ENDEAR): NCT021933074

   A phase III, randomised, double-blind, sham-procedure controlled study to assess the clinical efficacy and safety of ISIS 396443 administered intrathecally in patients with infantile-onset SMA.

2) Study CS4 (CHERISH): NCT02292537

   A phase III, randomised, double-blind, sham-procedure controlled study to assess the clinical efficacy and safety of ISIS 396443 administered intrathecally in patients with later-onset SMA.

3) Supportive studies:

   a. Study CS3A, a phase II, open-label study of Nusinersen, is being conducted at four centres in the USA and Canada (NCT01839656).

   b. Study CS1, a phase I, open-label, single-dose dose-escalation study, is being conducted to evaluate the safety, tolerability and pharmacokinetics of a single dose of Nusinersen administered intrathecally in subjects with SMA aged 2–14 years who were medically stable (NCT01494701).

   c. Study CS10 is an open-label study to evaluate the safety, tolerability and pharmacokinetics of a single dose of Nusinersen (6 or 9 mg) administered intrathecally in subjects with SMA who previously participated in study CS1 (NCT01780246).

   d. Study CS2 is a phase I/IIa, open-label, multiple-dose dose-escalation study designed to assess the safety, tolerability and pharmacokinetics of Nusinersen in 2- to 15-year-old subjects with SMA (NCT01703988).

   e. Study CS12 is an ongoing phase I, open-label, multiple dose study to assess the safety, tolerability and pharmacokinetics of repeated doses of Nusinersen (12 mg) administered intrathecally to subjects with SMA who previously participated in study CS2 or study CS10 (NCT02052791).

   f. Study SM201 (also known as CS5) is an ongoing phase II, open-label, multicentre, single-arm study to assess the efficacy, safety, tolerability and pharmacokinetics of Nusinersen in presymptomatic SMA (NCT02386553).

2.2 Assessment results and common evidence gaps

The synthesis of the main assessment results and evidence gaps identified at national level by different pilot team members is reported in Table 3. The synthesis points out outcomes for which evidence was commonly found to be of insufficient certainty or quality or was missing.

The recommendations for research arising from these evidence gaps are presented in Section 2.3.

Table 3. Assessment results for the effectiveness and safety domain

Study	Outcome 1	Outcome 2	Outcome 3	Outcome 4	Outcome 5	Outcome 6	Outcome 7
	Motor function	Time to death or permanent ventilation	Overall survival	Serious adverse events [a]	Proportion of patients who discontinued the treatment [b]	Health-related quality of life	Patients developing clinically manifest SMA (%)
Study CS3B Patients with infantile-onset SMA with a disease duration of <26 weeks at the start of treatment	1) Patients responding to the treatment, evaluated using HINE section 2 (motor milestones) [c] **- At interim analysis (mean follow-up 183 days): Nusinersen group 21/51 (41%), placebo group 0/27 (P<0.001)** **- At final analysis (394 days): Nusinersen group 37/73 (51%), placebo group (0/37)** 2) CHOP INTEND responders **Nusinersen group 52/73 (71%), placebo group 1/37 (3%); difference 68.53% (95% CI 51.27–81.99%)**	**HR 0.53 (95% CI 0.32–0.89); P=0.005**	**HR 0.372 (95% CI 0.18–0.77); P=0.004**	**No events**	**No events**	**No data**	**No data**
Certainty/quality of evidence [d]	High/moderate/low	Moderate/low	High/moderate	High/moderate	High/moderate	No data	No data
Study CS4-CHERISH Patients with Later-Onset Spinal Muscular Atrophy with a disease duration < 94 months	1) Variation in HFMSE at 15 months vs. baseline: **Least-squares mean difference in change 4.9 (95% CI 3.1–6.7)** [e] 2) Patients achieving a 3-point increase from baseline in HFMSE score at month 15 **Nusinersen group 57% vs. control group 26%; difference of 30.5% in favour of Nusinersen group (P<0.001)** 3) Subjects achieving ≥1 new WHO motor milestone: **Nusinersen group 20% vs. control group 6%; difference of 14% in favour of Nusinersen (P=0.08)**	**No data**	**No data**	**No events**	**No events**	**No data**	**No data**
Certainty/quality of evidence	Moderate/low	No data	No data	Moderate	Moderate	No data	No data

Study	Outcome 1	Outcome 2	Outcome 3	Outcome 4	Outcome 5	Outcome 6	Outcome 7
	Motor function	Time to death or permanent ventilation	Overall survival	Serious adverse events [a]	Proportion of patients who discontinued the treatment [b]	Health-related quality of life	Patients developing clinically manifest SMA (%)
Study CS5 Presymptomatic SMA with two or three *SMN2* copies	1) Participants attaining motor milestones assessed using part of the HINE: **All subjects had age-appropriate motor development measured using modified section 2 of the HINE** 2) Participants attaining motor milestones as assessed by WHO criteria **At least 1 WHO motor milestone achieved by: 1/11 subjects with 3 *SMN2* copies at day 64; 7/10 subjects (4 with 2 *SMN2* copies and 3 with 3 *SMN2* copies) at day 183; and 4/5 subjects with 2 *SMN2* copies at day 302.** 3) Change from baseline in CHOP INTEND motor function scale **An increase of at least 4 points in CHOP INTEND total score vs. baseline was observed for: 7/13 subjects (4 with 2 *SMN2* copies and 3 with 3 SMN2 copies) at day 64; 8/10 subjects (5 with 2 *SMN2* copies and 3 with 3 *SMN2* copies) at day 183; and 3/5 subjects with 2 *SMN2* copies at day 302**	**No events**	**All patients were alive at analysis**	**No events**	**No events**	**No data**	**Four subjects had manifestation of SMA symptoms on the basis of growth failure**
Certainty/quality of evidence	Very low	Very low	Very low	Moderate	Moderate	No data	Very low
Total studies assessing the outcome	3	2	2	3	3	0	1

[a] Serious adverse events that investigators considered to be related or possibly related to the study treatment.
[b] Because of adverse events investigators considered to be related or possibly related to the study treatment.
[c] Results from Finkel RS, Mercurio E, Darras BT, et al. Nusinersen versus sham control in infantile-onset spinal muscular atrophy. N Engl J Med 2017;377:1723–32.
[d] Certainty/quality of evidence as reported in the questionnaire by pilot team members.
[e] Results from Mercurio E, Darras BT, Chiriboga CA, et al. Nusinersen versus sham control in later-onset spinal muscular atrophy. N Engl J Med 2018;378:625–35.
Abbreviations: HINE=Hammersmith Infant Neurological Examination; HFMSE=Hammersmith Functional Motor Scale–Expanded; CHOP INTEND=Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; SMA=spinal muscular atrophy; WHO=World Health Organization.

2.3 Common research recommendations

The research recommendations arising from the evidence gaps identified and indicated by each pilot team member are reported in detail in the table 4 here below.

These research recommendations are reported according to the PICO scheme, as recommended in the guidance included in the position paper on how to best formulate research recommendations for primary research arising from HTA reports.

Of note, at this stage of the pilot for this report, the pilot team members reported all research recommendations as raised in their national assessment, regardless of the setting for collection of data (real world setting or clinical studies). The following step, dealing with the definition of a common data set, will specify the parameters to be analysed in the real world setting (e.g., patient characteristics at baseline by different SMA types).

In conclusion, most team members identified a need for the following further research:

- Full descriptive analysis considering patient characteristics at baseline by different SMA types (e.g., age at diagnosis, motor function at treatment initiation, etc.);
- Collection of data on long-term effects for all SMA types and on robust endpoints, as well as for less-studied subpopulations (e.g., SMA types IV and 0);
- Long-term safety data including reasons for discontinuation;
- Data on quality of life and other patient-reported outcomes;
- Data on treatment duration and sequence and the most appropriate dose to be used for different patient groups;
- Data on the number of patients treated; and
- Validation of new outcome measures for disease progression.

Table 4. Compiled research recommendations according to the PICO

	Population	Intervention	Comparator*	Outcome	Other questions
1	SMA I - disease diagnosed less than 26 weeks before the start of treatment - disease diagnosed later than 26 weeks before the start of treatment	To collect data on the most appropriate dose	Natural progression of the disease	Longer term treatment for outcomes 1-5 from Table 3	
2	SMA I and more than 2 SMN2 gene copies	To collect data on the most appropriate dose	Natural progression of the disease	Outcome 1-5 from Table 3	
3	SMA II - disease diagnosed less than 94 months before the start of treatment - disease diagnosed later than 94 months before the start of treatment		Natural progression of the disease	Longer term treatment for outcomes 1-5 from Table 3 Outcomes 1-5. -no deterioration on the HFMSE-score	
4	SMA II and more than 3 SMN2 gene copies'	To collect data on the most appropriate dose	Natural progression of the disease	Outcomes 1-5 from Table 3 More research evidence if patients are to be treated purely based on genetic testing without symptoms	
5	SMA III	To collect data on the most appropriate dose	Natural progression of the disease	Outcomes 1 -5 - For patients ≥4,5 years: - no deterioration on the HFMSE-score instead of proportion of participants who achieved a 3-point increase from baseline in HFMSE -- Score at month 15 and subjects achieving new WHO motor milestones.	

	Population	Intervention	Comparator*	Outcome	Other questions
6	SMA IV	Nusinersen	Natural progression of the disease	Outcomes: Longer term treatment for outcomes 1-6 from Table 3 Need for validated instrument to measure motor function in adult patients- special focus on upper limb functions.	
7	Pre-symptomatic infants genetically diagnosed with 5q SMA and with: - 2 or 3 SMN2-copies - another number than 2 or 3 SMN2-copies	To collect data on the most appropriate dose	Natural progression of the disease	Longer term treatment for outcomes 1-5 and 7 from Table 3	
8	All users of Nusinersen. Patients already on mechanical ventilation.	Nusinersen Administration under sedation (yes/no)	Natural progression of the disease	Longer term treatment for 1-7 outcomes from Table 3 Use of permanent ventilation; and for patient already at permanent ventilation: effect of Nusinersen on the number of hours and time of day spent on ventilation	• Reason for discontinuation • Treatment duration • Baseline characteristics (demographic; clinics) • Patients/informal caregivers views; • Providers views; • Legal and ethical issue related to serious AEs in patients received drug with accelerated approval • Number of hospitalization • time spent in hospital; • lumbar puncture administration (procedure) failure • Cost-effectiveness or Cost-utility analysis

*any additional therapeutic options which will be available will be considered as comparators.

APPENDIX 1. CLINICAL CLASSIFICATION OF SPINAL MUSCULAR ATROPHY (SMA)

SMA type/incidence	Onset (age)	Need for respiratory support at birth (yes/no)	Ability to sit	Ability to stand	Ability to walk	Life expectancy	Number of SMN2 gene copies
0/Very rare	Prenatal	yes	no	no	no	<6 months	1
I (around 58%)	<6 months	no	no	no	no	<2 years	2
II (around 29%)	6-18 months	no	yes	no	no	10-40 years (70% alive	3 (80%)
III (around 13%)	>18 months	no	yes	yes	with assistance (wheelchair)	Adult age (normal lifetime)	3-4 (80% has 4 copies)
IV (<5%)	>30 years	no	yes	yes	yes	Adult age (normal lifetime)	>4

Adapted from Bodamar OA. Spinal muscular atrophy. UpToDate, July 2017

APPENDIX 2. QUESTIONNAIRE ON EVIDENCE GAPS TEMPLATE

Agency	
Country	
Contacts	
HTA assessment status	□ Finalised □Ongoing Further comments: free text
Evidence gaps identified in the HT assessment	Please indicate the domain in which evidence gaps have been identified during HTA (Multiple answers are possible if needed): □Clinical effectiveness □Safety □Cost effectiveness □Budget impact □Condition of use □Personnel recruitment and training □ Others (please specify)
Research question	Please provide the details on the evidence gaps and the research question(s) according to the following template:

Evidence gaps				
Assessment results				
For each outcome, specify the main assessment results in terms of the quality and quantity of available evidence (number of studies, type of studies), and, if applicable, the estimate of the effect size and the level of confidence in the estimate. ***Please clarify the evidence gaps for each outcome of your assessment, sorted by the level of importance:***				
Outcome- level of importance 1	Outcome- level of importance 2	Outcome- level of importance 3	Outcome- level of importance 4	Outcome- level of importance 5
Recommendations for research				
Question with clear rationale: potential relationship between intervention and important outcomes. ***Please report the research question, for each evidence gap reported here above, according to the PICO.*** ***Additional questions should be presented in the column "Other questions".***				

Population	Intervention	Comparator	Outcomes	Time Stamp	Other questions
Population or sub population of interest. *Example: to collect data patients with a mild, adult onset course (previously categorized as type IV SMA)*	The technology/intervention and setting of use *Example: To collect data on the most appropriate dose to be used for the different patients*	Relevant comparator and setting of use	Outcomes of interest (1-5) *Example: To collect long term efficacy data*	Date when the recommendation was issued, alternatively the date of the HTA assessment finalization or the date when this form has been filled out	E.g. number of patients, duration of treatment

Table adapted from the "Position Paper on how to best formulate research recommendations for primary research arising from HTA"

https://eunethta.eu/wp-content/uploads/2019/10/EUnetHTA-Position-Paper-on-research-recommendations.pdf

SOURCES

- Assessment Report (EPAR) Spinraza Procedure No. EMEA/H/C/004312/0000
- ClinicalTrials.gov A Study to Assess the Efficacy and Safety of Nusinersen (ISIS 396443) in Infants With Spinal Muscular Atrophy (ENDEAR). Available at: https://clinicaltrials.gov/ct2/show/NCT02193074
- ClinicalTrials.gov A Study to Assess the Efficacy and Safety of Nusinersen (ISIS 396443) in Participants With Later-onset Spinal Muscular Atrophy (SMA) (CHERISH) Available at: https://clinicaltrials.gov/ct2/show/NCT02292537
- ClinicalTrials.gov A Study of Multiple Doses of Nusinersen (ISIS 396443) Delivered to Infants With Genetically Diagnosed and Presymptomatic Spinal Muscular Atrophy (NURTURE) Available at: https://clinicaltrials.gov/ct2/show/NCT02386553
- Position Paper on how to best formulate research recommendations for primary research arising from HTA https://eunethta.eu/wp-content/uploads/2019/10/EUnetHTA-Position-Paper-on-research-recommendations.pdf
- E. Mercuri et al. Nusinersen versus Sham Control in Later-Onset Spinal Muscular Atrophy. N ENGL J MED 378;7 February 15, 2018
- R.S. Finkel et al. Nusinersen versus Sham Control in Infantile-Onset Spinal Muscular Atrophy. N ENGL J MED 377;18. November 2, 2017