Available online at www.sciencedirect.com
ScienceDirect
Neuromuscular Disorders xxx (xxxx) xxx
www.elsevier.com/locate/nmd

Understanding European patient expectations towards current therapeutic development in spinal muscular atrophy

Nicole Gusset[a,b,*], Caroline Stalens[c], Eva Stumpe[a,d], Lori Klouvi[c], Alexandre Mejat[a,c], Marie-Christine Ouillade[a,c], Mencía de Lemus[a,e]

[a] SMA Europe, Im Moos 4, 79112 Freiburg, Germany
[b] SMA Schweiz, Alpenstrasse 76, CH – 3627 Heimberg, Switzerland
[c] AFM Telethon, 1 rue de l'Internationale, 91002 Evry, France
[d] Deutsche Gesellschaft für Muskelkranke, Im Moos 4, 79112 Freiburg, Germany
[e] FundAME, Calle Antonio Miró Valverde, 5°G, 28055 Madrid, Spain

Received 26 August 2020; received in revised form 24 January 2021; accepted 29 January 2021
Available online xxx

Abstract

Following the 2017 approval of a first spinal muscular atrophy (SMA) treatment by the European Medicines Agency, SMA Europe launched a Europe-wide survey with the goal of understanding patients' treatment expectations, realities of daily living and access to clinical trials and therapy, and how this varied according to parameters such as age and disease severity. A response rate of 31% yielded 1474 completed surveys from 26 European countries. In line with findings from a 2015 SMA Europe-led survey, participants considered stabilization of their condition to be progress. Notably, responses indicated that the current classification of SMA at diagnosis by 'type' often does not reflect current mobility level. Large gaps in treatment access were identified that varied in particular between age and disease severity groups, yet there was high interest in clinical trial participation. In addition, alternative treatment options, including combination therapies, are now expectations. These perspectives should be central considerations through the research and development processes of new SMA therapies, through data generation and discussions on access to therapies. Results from this survey indicate that collaboration between stakeholders is essential to the foundation upon which innovative approaches for SMA treatments and access can be explored.
© 2021 Elsevier B.V. All rights reserved.

Keywords: Spinal muscular atrophy; SMA Europe; Survey outcome; Patient's perspective; Evidence-based patient advocacy; Individual optimal therapeutic benefit.

1. Introduction

Spinal muscular atrophy (SMA) is a rare, autosomal recessive neuromuscular disorder occurring in approximately 1 in 10,000 live births [1]. Characterized by degeneration of motor neurons, SMA leads to progressive muscle weakness and atrophy [2,3]. It is caused by homozygous mutations in survival of motor neuron 1 gene (*SMN1*) resulting in SMN protein deficiency [2–4]. A closely homologous gene, *SMN2*, has variable copy numbers (with greater copy number being associated with lower disease severity [5]) and also produces SMN protein. However, most of this protein is unstable, with one copy producing just ~10–15% of the required functional protein [2,6].

At diagnosis, the broad spectrum of SMA phenotypes are classified into clinical types based on age of onset and maximum motor function ever achieved: Type 0 (usually fatal at birth); Type 1 (unable to sit independently); Type 2 (able to sit independently but not walk); Type 3 (independent walking) and Type 4 (independent walking and adult onset) [2]. However, variations in disease progression and disease heterogeneity regardless of type have been evidenced by natural history studies [7], therefore SMA management recommendations in the rehabilitation phase are based on the current mobility level of patients; that is, whether they are a non-sitter, sitter or walker [8,9].

* Corresponding author at: SMA Schweiz, Alpenstrasse 76, CH – 3627 Heimberg, Switzerland.
E-mail address: nicole.gusset@sma-europe.eu (N. Gusset).

https://doi.org/10.1016/j.nmd.2021.01.012
0960-8966/© 2021 Elsevier B.V. All rights reserved.

Please cite this article as: N. Gusset, C. Stalens, E. Stumpe et al., Understanding European patient expectations towards current therapeutic development in spinal muscular atrophy, Neuromuscular Disorders, https://doi.org/10.1016/j.nmd.2021.01.012

The lives and independence of individuals with SMA are heavily impacted [10,11]. Symptoms such as muscle weakness, reduced stamina and fatigue make it difficult for patients to carry out everyday tasks, such as chewing and swallowing food, or operating power wheelchairs for prolonged periods of time [12]. In addition, basic physical functions such as respiration may be affected, resulting in a need for assisted ventilation [13], and orthopedic difficulties frequently arise as a result of contractures and scoliosis [14,15]. Due to these challenges, patients and caregivers experience physical, psychological, social and financial burdens [10,16–22]. It is therefore important that the impact of SMA across phenotypes, as well as the impact of clinical interventions on quality of life, are better understood [23].

1.1. Current treatment and standard of care in SMA

To date, no cure has been developed for SMA. However, three SMA treatments received US Food and Drug Administration (FDA) or both FDA and European Medicines Agency (EMA) approval between 2016 and 2020: nusinersen (SPINRAZA®) [24,25], an intrathecally administered antisense oligonucleotide (ASO) that alternatively splices *SMN2*, enabling it to produce a greater amount of functional SMN protein, onasemnogene abeparvovec-xioi (Zolgensma®) [26,27], an intravenous gene therapy that delivers a functional copy of the human *SMN* gene [28], and risdiplam (Evrysdi™) [29], an oral *SMN2* pre-mRNA splicing modifier. There are also many other drugs in development with varying mechanisms of action and administration routes [30].

In 2007, prior to the availability of treatments, a consensus on the standard of supportive care in SMA was established by the International Standard of Care Committee for Spinal Muscular Atrophy [31], followed by a new edition in 2018 [9,32]. It advised that standardized patient care should involve physiotherapy and orthopedic care (e.g., management of scoliosis and contractures, and provision of wheelchairs and orthotics), pulmonary care (e.g., assisted ventilation), nutritional support, and palliative care [9,32–34]. Studies have suggested such supportive approaches benefit patient outcomes [17,35], highlighting the importance of ensuring availability of these interventions for all patients in the SMA community who require them.

1.2. Unmet therapeutic needs and challenges in the SMA community

Despite recent advances in pharmacologic and non-pharmacologic interventions in SMA, there are ongoing unmet therapeutic needs such as access to treatment, alternative treatment options and combined or add-on therapies [34,36].

Although treatment efficacy of approved therapies has been mainly demonstrated in infants with Type 1 SMA [37–39], recent studies have shown that older children and adults may benefit [40,41]. Despite this and a broad EMA approval, access to nusinersen is often restricted by age or SMA type [25] or not available at all in some countries. Intrathecal administration of nusinersen can be associated with complex logistical requirements [42,43], contributing to patient and caregiver burden, and the procedure itself can be difficult to perform [44]. Furthermore, recent studies indicate a need for complementary therapies addressing SMN-independent pathogenic pathways [45] and an emerging rationale for use of substances to improve muscle function alongside drugs that restore SMN protein [46–48].

1.3. Evidence-based patient advocacy: patient expectation survey

It has been highlighted that involving expert patients and patient organizations in decision-making in the research and development of medicines from an early stage contributes to the improvement of outcomes, health service delivery, and practice and policy implementation [49–51]. Examples of expert patient involvement can include setting research priorities; providing insights on disease burden, unmet needs, expectations of the patient community; and optimization of clinical study design and endpoint development [49,50,52].

Evidence from patients can be collected through a variety of methods such as Focus Groups, one-to-one interviews, Patient Panels and surveys. In 2015, SMA Europe, an umbrella organization of SMA patient organizations across Europe, conducted a large-scale multinational survey to assess the impact of SMA on general well-being and the therapeutic expectations of patients with Type 2 and Type 3 SMA in Europe. Through this we learnt that almost all respondents (96.5%) considered stabilization to be a positive outcome from treatment, regardless of disease status, age or geographical origin [35]. In 2017, McGraw, et al. showed that a meaningful change in SMA was relative to functional ability, and that even small changes in motor function, such as having a small degree of finger movement to operate a power wheelchair, may have a large impact on quality of life [53].

1.4. Patient advocacy tool: second european patient expectation survey (EUPESMA-2019)

Following the identification of persisting unmet needs in access, treatment options and quality of life, SMA Europe aimed to build upon the findings of the 2015 survey [35], when no treatment was available, with a second European Patient Expectation Survey in 2019 (EUPESMA-2019), when a first treatment was available. This survey was designed to further understand patient treatment expectations and well-being among those treated with nusinersen versus those untreated; to assess expectations relative to age and disease severity; and to identify restrictions to involvement in clinical trials and access to approved therapies.

Here we describe insights from the survey, which will be used as an evidence-based advocacy tool to facilitate improved patient access to treatment and support the research

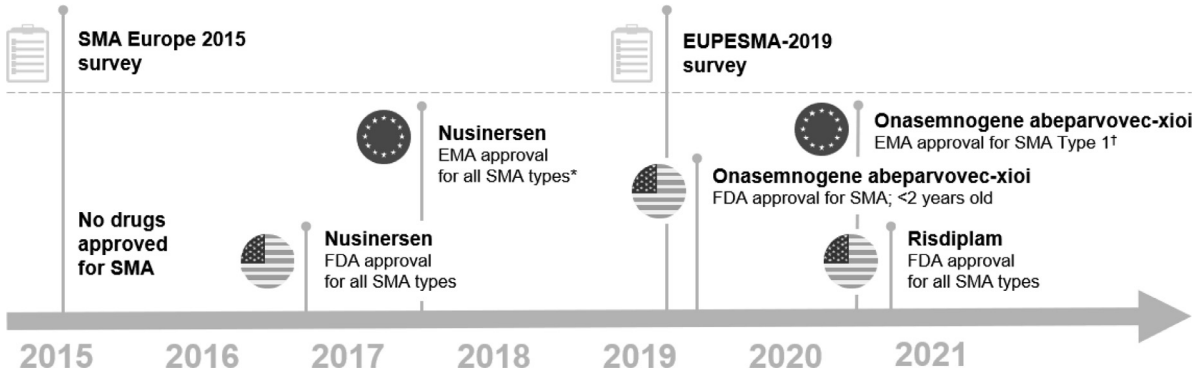

Fig. 1. Timeline of approval of current SMA treatments and start dates of SMA Europe patient surveys. *5q SMA in paediatric and adult patients with some variations in reimbursement across countries, e.g., for Type 1, 2, 3, 4 (excluding IV) and in some cases including age restrictions such as <18 years old. † Or have up to three copies of *SMN2*. EMA, European Medicines Agency; FDA, Food and Drug Administration; SMA, spinal muscular atrophy; *SMN2*, survival of motor neuron 2.

and development of additional therapeutic approaches in SMA.

2. Material and methods

Based on an extensive literature review including the first survey from 2015, as well as the feedback from an SMA Europe representative group of expert patients and carers, SMA Europe developed the EUPESMA-2019 questionnaire. EUPESMA-2019 consisted of 44 questions divided into six categories: demographics, education and employment, mobility and health status, SMA medical treatment, clinical trials, and well-being and expectations (see Supplementary materials for more details).

Member organizations translated the cover letter explaining the purpose of the survey, the consent-to-access and the survey into 16 languages followed by distribution across 19 European member countries: Belgium, Czech Republic, Denmark, Finland, France, Germany, Ireland, Italy, North Macedonia, The Netherlands, Poland, Romania, Russia, Serbia, Spain, Sweden, Switzerland, UK and Ukraine. Some of these organizations may also include members from other countries.

The survey was launched on 9 July 2019 and was aimed at European SMA patients of all ages and disease severity (Fig. 1). It was distributed by SMA Europe member organizations online through personal emails with an access link to their SMA patients, preceded by preferred language selection, a cover letter, and a consent-to-access questionnaire. Data were collected and hosted by COGVIO. Results were anonymous and could not be assigned to a specific participant. The survey was not distributed on social media platforms to ensure participation was specific to the SMA community.

Partially completed questionnaires were not included in the analysis. Cross-analysis of responses was conducted after stratification as indicated in Supplementary Table 1.

The statistical analysis was conducted using descriptive statistics and comparative statistics including chi-square test for the qualitative variables assessed in this report. For each item, subgroup analyses were carried out to determine whether answers were significantly different between patient treatment status, SMA types, age groups, mobility levels and responder type (patient or parent). All tests were two sided and the threshold for statistical significance was set at 0.05. Analyses were performed using SAS® software version 9.4.

3. Results

3.1. Overview of the respondent population

3.1.1. Demographics

SMA Europe sent the questionnaire to 4749 patients. 2253 questionnaires were returned of which 765 were partially completed and 14 were duplications. 1474 were included in the final analysis, giving an overall response rate of 31%. While surveys were disseminated to individual members of the 19 SMA Europe national member organizations, participants originating from 26 European countries responded overall (Supplementary Table 2), demonstrating the mobilization of SMA communities across Europe.

Participants ranged from 0–81 years old (mean [standard deviation; SD]= 24.0 [19.1]). Most participants were patients (52.6%) or parents on behalf of patients (47.2%); in 0.3% of cases, a non-parental caregiver responded on behalf of the patient.

3.1.2. Mobility level

Most participants were sitters (43.1%) or non-sitters (43.6%); only 13.2% were walkers. Notably, each mobility level included participants with SMA Types 1–4 (Fig. 2), reflective of types globally [54].

A fifth (19.7%) of participants reported that they currently use a manual wheelchair, which they are able to move independently; 16.3% previously had this ability but had later lost it at the mean (SD) age of 16.3 (10.8) years. Almost a quarter (23.0%) of participants stated they use a manual

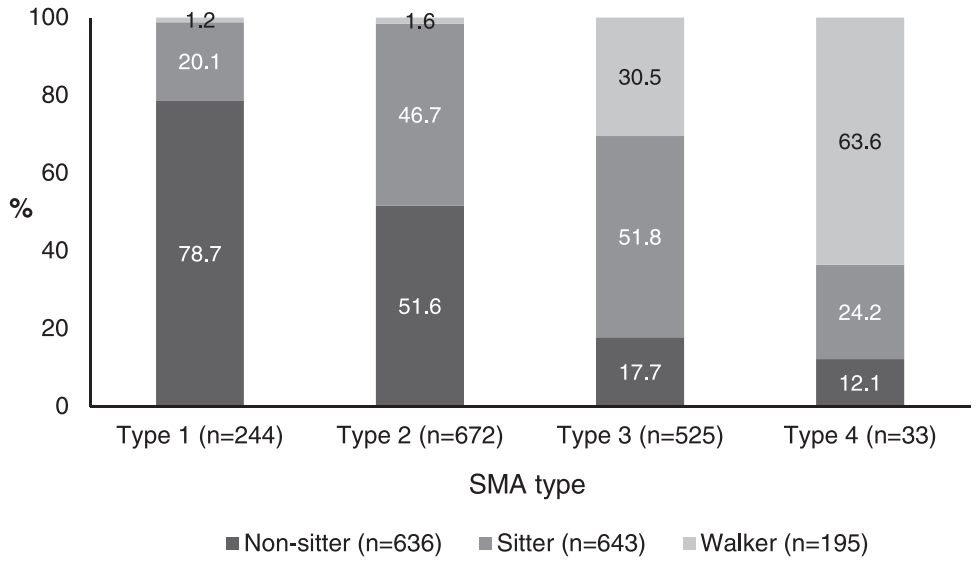

Fig. 2. Distribution of participants mobility level by SMA type. Percentage of responses stratified by patient mobility level and SMA type. Histograms represent the percentage of participants in each mobility level. SMA, spinal muscular atrophy.

wheelchair or buggy but cannot use it independently. Over half (57.7%) of the participants use a power wheelchair, while 1.4% had previously, but had lost the ability at the mean (SD) age of 20.5 (14.3) years.

3.1.3. Scoliosis, contractures and respiratory function

56.4% of participants had scoliosis. Half (48.7%) of the participants had received some form of therapy or surgery for scoliosis, which included wearing a brace (22.0%), requiring growing rods (7.1%), or having undergone a spinal fusion (19.6%). There was a lower occurrence of scoliosis in participants who were more mobile, when stratified by mobility level; 65.9% of non-sitters, 52.4% of sitters, and 39.0% of walkers. Contractures occurred frequently throughout the body, with regularly used joints according to mobility level particularly affected. Overall contractures were most common in the knees (63.4%), followed by the hips (39.8%), elbows (32.2%), jaw (21.0%), wrists (19.1%), and shoulders (18.1%). Patients reporting 'other' contractures (18.0%) indicated these being in the hands, fingers, feet, and neck. Differences in expression of scoliosis, contractures and ventilation between SMA types and mobility levels are described in Table 1.

When asked about the status of their respiratory function, most participants did not require assisted ventilation (69.1%). Of those who required assistance, 80.7% used non-invasive ventilation (NIV) and 19.3% had a tracheostomy. Only 4.3% of the participants who needed NIV reported using it $\geq$ 16 hours per day. Ventilation requirements differed significantly across mobility levels and SMA type with 52.2% of non-sitters, 19.0% of sitters and just 0.5% of walkers requiring ventilation ($P<0.001$). When stratified by SMA type, 67.2% of those with Type 1 SMA, 37.4% with Type 2 SMA, 7.0% with Type 3 SMA and 9.1% with Type 4 SMA required assisted ventilation ($P<0.001$).

3.1.4. Education and employment

21.9% of participants were not yet at school at the time of survey completion; of those with school education, 41.3% reported their education as ongoing.

Almost half (44.5%) of those who were >18 years old were employed. Half (48.7%) of the participants >18 years old had received tertiary education, with a third (31.1%) of the 26–40 age group having achieved a master's degree or doctorate. Further detailed assessment of age groups >18 years old revealed that present involvement in education peaked in the younger group (62.0%; 28.3% in employment) and involvement in employment peaked between 26–40 years old (58.6%; 11.3% in education), with both decreasing beyond 40 (2.6% in education, 39.9% in employment).

3.2. Understanding patients' therapeutic expectations

3.2.1. Access to approved treatments

Three quarters (73.2%) of participants were not receiving an approved treatment at the time of survey completion (Fig. 1). Most participants receiving treatment did so through reimbursement (85.8%), the rest through early access programs (EAPs) (13.9%), clinical trials (5.6%) or other means (3.8%). For participants who had not received treatment, when asked "Why have you not started the approved treatment?", only 5.3% reported not wanting treatment. Lack of access was a common reason for not receiving treatment (treatment was not available in their country [35.6%]; the treatment was available, but participants did not have access to it [25.9%]; participants had scoliosis or a spinal fusion that prevented treatment administration [13.6%]).

Table 1
Relative division of all participants with scoliosis, contractures in specific joints, or need for assisted ventilation according to SMA type and mobility level. Differences in expression of a complication between SMA type and the classical corresponding mobility level are highlighted. SMA, spinal muscular atrophy.

		Complication; relative %							
	n	Scoliosis	Hip	Knees	Shoulders	Elbows	Wrists	Jaw	Ventilation
Type 1	*244*	29.2	30.7	32.6	35.5	40.3	41.5	45.2	55.7
Non-sitter	*636*	41.9	57.1	52.9	71.8	72.1	74.7	78.5	72.8
Difference		*+12.7*	*+26.4*	*+20.3*	*+36.3*	*+31.8*	*+33.2*	*+33.3*	*+17.1*
Type 2	*672*	32.8	46.7	42.2	38.1	47.0	42.0	41.5	31.0
Sitter	*643*	33.3	39.1	39.5	23.3	25.2	19.6	19.5	26.5
Difference		*+0.5*	*−7.6*	*−2.7*	*−14.8*	*−21.8*	*−22.4*	*−22*	*−4.5*
Type 3	*525*	26.9	21.8	22.1	12.3	12.8	7.3	8.8	5.8
Type 4	*33*	11.1	0.9	3.1	14.0	0.0	9.2	4.5	7.5
Walker	*195*	24.8	3.8	7.6	4.8	2.8	5.7	2.0	0.7
Difference[*]		-2.1	-18	-14.5	-7.5	-10.0	-1.6	-6.8	-5.1
Difference[**]		+15.8	+2.9	+4.5	-9.2	-2.8	-3.5	-2.5	-6.8

[*] Difference between the disease assessment category Type 3 and walkers
[**] Difference between the disease assessment category Type 4 and walkers

Table 2
Relative division of all participants who want access to a therapy into those who have access and those who have no access. Treatment access in each age group, by SMA type, and by mobility level is shown, with opposite results for SMA type and the classical corresponding mobility level. SMA, spinal muscular atrophy.

	n	wanting a treatment but no access; relative %	on treatment; relative %
Participants who want access to a therapy	*1417*	72.1	27.9
Age (years)			
<2	*58*	55.2	44.8
2-5	*229*	48.9	51.1
6-11	*251*	59.8	40.2
12-17	*148*	70.3	29.7
18-25	*155*	84.5	15.5
26-40	*274*	81.0	19.0
>40	*302*	89.7	10.3
SMA Type			
Type 1	*237*	55.3	44.7
Type 2	*649*	73.0	27.0
Type 3	*498*	77.1	22.9
Type 4	*33*	100.0	0.0
Mobility level			
Non-sitter	*606*	77.2	22.8
Sitter	*620*	68.9	31.1
Walker	*191*	66.5	33.5

Overall, 69.3% of participants, including those of all age groups, SMA types and mobility levels, did not have access even though they wanted it (Table 2).

Insufficient access to the approved therapy resulted in reports of strong negative feelings (2636 emotions [87.7%] of total cited, whereby the participants were able to give multiple responses), which included: anger, frustration, helplessness, traumatization, unfair treatment, and devastation. More than half of the participants felt helpless and/or frustrated (59.6% and 56.8%, respectively) and almost half felt unfairly treated (46.2%).

3.2.2. Expectations of drug target and administration

To understand expectations surrounding treatment targets, participants were asked "What do you think a therapy should target?". Participants were asked to select any options they believed to be important. Combination therapy had the biggest support (77.0%), with participants showing very similar favor (approximately 60%) towards "The gene (*SMN1* gene therapy)", "*SMN2* splicing", and "Muscle strength and capacity" (muscle enhancer), and with 39.8% in favor of targeting "Respiratory function (breathing)".

Participants showed a high acceptance for all three routes of drug administration (intrathecal, intravenous and oral), although there was a significant difference in willingness to accept intrathecal administration between the treated and untreated groups (85.8% vs. 52.8%; P<0.001) (Fig. 3).

3.2.3. Expectations towards clinical trials

A total of 13.5% of participants had taken part in a clinical trial; over half of those were enrolled at the time of the survey (55.1%). Of those who had never participated, it was reported by most that this was because there were no study sites in their country (31.5%) or their age did not meet the inclusion criteria (28.5%). For others, they did not have the required level of motor function (9.2%); they could not travel to the study site (6.7%); the clinical trial was already full (5.8%); or they could not fit the study timetable around their personal situation (3.8%) – 20.6% selected 'other reasons'; among those were patients that had not been asked or that were afraid. As with responses from those not able to get access to treatment, 81.9% of responses indicated strong negative feelings associated with not being eligible for a clinical trial.

High interest (84.3%) was shown for clinical trial participation. Both treated and untreated patients showed high interest in participating in a clinical trial, with a small but

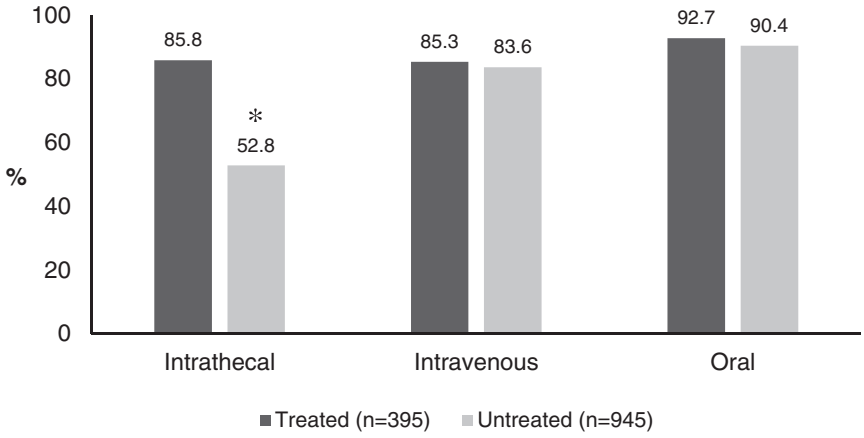

Fig. 3. Willingness of participants to accept different routes of administration. Percentage of participants who were willing to accept each administration route stratified by treatment status. *P<0.001 by chi-square test.

Table 3
Views on clinical trial participation, stratified by treatment status.

	Treated	Untreated	All participants
Are you interested in participating in a clinical trial?			
	n=393	n=940	n=1465*
Yes	80 (20.4%)	701 (74.6%)	858 (58.6%)
Yes, but I would not want to stop the current treatment	224 (57.0%)	37 (3.9%)	296 (20.2%)
Yes, I would consider stopping the current treatment and switch to another therapy that is under investigation	38 (9.7%)	33 (3.5%)	81 (5.5%)
No	51 (13.0%)	169 (18.0%)	230 (15.7%)
Would you enter a clinical trial for which you know there is a placebo arm?			
	n=340	n=768	n=1230†
Yes	42 (12.4%)	180 (23.4%)	251 (20.4%)
Yes, but only if I get the active substance after, if the trial is successful	69 (20.3%)	232 (30.2%)	331 (26.9%)
Yes, but only if I get the active substance after, if the trial is successful. However, if my condition deteriorates considerably during the trial, I would want to be shifted onto the active substance‡	146 (42.9%)	271 (35.3%)	449 (36.5%)
No	83 (24.4%)	85 (11.1%)	199 (16.2%)

* Including those who were treated/untreated/treatment status unknown and responded to the question regarding clinical trial participation.
† Including those who were treated/untreated/treatment status unknown and indicated interest in participating in a clinical trial.
‡ This question was purely hypothetical with a focus on potential patients' needs, disregarding current standards set by the FDA and EMA.

significantly higher proportion of interest from the treated population (87.0% vs. 82.0%; P=0.025) (Table 3).

When asked about taking part in clinical trials with placebo arms, only 16.2% of those prepared to participate in a clinical trial overall reported they would refuse. However, 63.4% would only be willing to participate if they were eventually able to receive the active substance. Significantly fewer treated than untreated participants were willing to participate in clinical trials with a known placebo arm (75.6% vs. 88.9%; P<0.001). (Table 3).

3.2.4. Expectations of therapeutic outcome – stabilization

Nearly all participants stated that they would consider stabilization to be relevant therapeutic outcome. Participants where asked, "If there was a drug to stabilize your current clinical state, would you consider this to be progress?" The overwhelming majority (96.6%) responded "Yes", a trend echoed across all treatment categories (Table 4).

4. Discussion

The therapeutic environment in SMA is changing fast. Before 2017, not a single treatment was available in Europe. In the last 3 years we have seen EMA approval of two therapies, with others imminent. Throughout this period, SMA Europe has continued to support the vital relationship between patients and all respective stakeholders, to ensure the best outcomes for the SMA community. Integral to this was the 2015 survey on patient expectations, which we now follow up with EUPESMA-2019. Through this we gauge the current expectations of patients given their expanded options.

Table 4
Participants' views on stabilization, stratified by treatment status, age group, responder type, mobility level and SMA type.

		n	Stabilization considered progress (%)
Overall		1474	96.6
Treatment status	Treated	395	95.2
	Untreated	945	97.2
Age (years)	<2	59	98.3
	[2–5]	229	93.9
	[6–11]	254	97.2
	[12–17]	150	99.3
	[18–25]	168	95.8
	[26–40]	296	97.0
	>40	318	96.5
Responder type	Patient	775	96.5
	Parent	699	96.7
Mobility level	Non-sitter	636	96.5
	Sitter	643	96.6
	Walker	195	96.9
SMA type	1	244	92.6
	2	672	97.9
	3	525	96.8
	4	33	97.0

4.1. Demography

This study included a broad spectrum of SMA patients across Europe, from infants to adults, with differing mobility levels. Most participants were sitters and non-sitters, with fewest being walkers (see 4.2).

Scrutinizing demographics provided insights into the huge impact SMA has on quality of life. Patients and their carers living with SMA must adapt to the increasing loss of independence – as indicated through reduced employment for older patients and the fact that many had once been able to use a manual wheelchair but no longer could. Yet a large proportion of participants were affected by disease manifestations such as scoliosis and the need for a tracheostomy, which prevented access to clinical trial involvement and/or treatment.

4.2. SMA type versus mobility level

SMA is a 'spectrum disease' where patients experience disease progression. As such, for each SMA type, all three mobility levels were reported, with similar patterns reported by other recent studies as well as the first SMA Europe-led survey in 2015 [35,39,55–58]. For example, despite those with Type 1 SMA classically being defined as non-sitters, many were sitters, and of those with Type 3 SMA, classically defined as walkers, many could not walk; and in addition, the expression of complications such as scoliosis, contractures or ventilation between SMA type and the classical corresponding mobility level is different. This suggests that type alone is not a reliable criterion for assessing the severity of disease or its progression.

Discussion of trial results based on a classification given at diagnosis is therefore challenging, yet it persists, leading to substantial problems for patients relating to treatment access as well as eligibility to participate in clinical trials or EAPs. Moreover, as a rare disease, the lack of clinical experience when assigning a diagnosis of Type 1-4 leave open the possibility of diagnostic errors. Furthermore, new phenotypes emerging with the advent of new treatments have been observed [59]. Patients with disease onset before 6 months of age, for example, can now achieve 'sitter' status due to early treatment initiation [30], effectively transitioning between types.

Classifying patients into types will never fully serve individuals affected by a spectrum disease such as SMA. Research shows that although the disease has a monogenic origin, other factors mean that the manifestations are highly complex. For example, correlation between *SMN2* copy number and the clinical phenotype is not always predictable; peripherally available tissues show variations in SMN protein levels as well as discrepancies in correlation with *SMN2* copy number, and genetic modifiers have been noted to influence disease severity and symptoms [36]. A consensus on how to move forward with a classification of SMA is needed, and this should fully reflect individual patient circumstances and needs.

4.3. Stabilization

If the natural course of disease over time is deterioration, stabilization might be considered a highly successful treatment effect. Indeed, this survey strongly confirms the finding of the 2015 survey by SMA Europe [35] that individuals living with SMA consider stabilization of their current clinical state to be progress, with 96.6% of all participants in agreement and the proportion similar across stratified groups.

Despite this, recent discussions have highlighted the need for careful clinical counselling to manage the therapeutic expectations of patients and their families [36], as expectations are influenced by external sources that may exaggerate potential benefits [60,61]. Given the increasing media attention surrounding the SMA therapeutic environment, there is a responsibility for clinicians, patient organizations and other stakeholders to manage expectations, especially those of newly diagnosed families. It should be expected that responses to treatment will vary between individuals [37–39,62].

Given the progressive nature of SMA, patients and families express sadness and fear at the prospect of gradually losing functional ability, and with it the ability to perform everyday activities independently (to be discussed in more detail in future publications) [51]. Further to being progressive, SMA is unpredictable [55]. Therefore, as with other progressive neurological disorders such as Parkinson's disease, Duchenne muscular dystrophy and multiple sclerosis, not knowing if or when to expect a loss of functional ability results in a need for frequent adaptation. This can lead to loss of control, and by extension, independence. Consequently, planning becomes difficult, social lives become restricted and

emotional well-being of individuals is negatively affected [10,63–67]. The prospect of the condition not worsening is clearly important across the SMA community and should be taken into consideration when assessing the effectiveness of therapies.

4.4. Access to approved treatments

Financial considerations can influence treatment access and are a leading factor behind inequalities [68]. As there is no consensus in Europe on how to determine the price of an orphan drug, costs vary between countries [69]. Results from this survey show unequal treatment access across different age groups, SMA types and mobility levels, with the trends between access and either type or mobility severity level lacking in alignment. The study also highlights the frustration felt by the participants on access issues. In response, some patients and their families may pay for treatment via fundraising initiatives, while others move to countries where they have access to clinical trials or treatment is available, leaving social safety nets behind [70]. The global SMA community is well connected; experiences and information on treatments are shared online. This means synchronized access to treatments is highly important to avoid frustration.

Many countries restrict access to pharmacologic treatment to the population assessed in associated clinical trials [34]; there is a need to provide data supporting use in other populations. Studies have suggested that SMN-targeted therapies should be administered as early as possible in the disease course to produce maximal therapeutic benefits [39,58,62,71]; but older, chronic patients may still benefit, as shown in real-world and more recent clinical trials [40,41]. The definition of 'optimal therapeutic benefit' varies according to the perspective. For drug developers and payors in the health sector, it means the best possible outcome that can be achieved on average; for individual patients, the term reflects what they can achieve personally – regardless of disease stage ('individual optimal therapeutic benefit').

4.5. Drug targets and administration

This study shows that participants are in favor of combination therapy and the need for additional treatment approaches is high.

As SMN protein is ubiquitously expressed, SMA is considered a multisystem disease [59,72,73]. The compound benefits of peripheral and central application of an ASO treatment were demonstrated in mice by Hua et al. [74]. Additional experiments in mice showed further benefits from myostatin inhibitors in combination with an ASO or small molecule [46-48]. However, there is a lack of clarity on this.

This survey shows that participants have a high willingness to accept intrathecal, intravenous and oral administration of therapeutics, with a notable preference for less invasive and burdensome applications, which may also be characteristic of the current lack of treatment options in SMA. While there is significantly more acceptance for less invasive administration techniques among those who are untreated, acceptance for more burdensome procedures is likely if a compound is effective.

The challenges of intrathecal application are summarized by Schorling et al. [30]; it can be particularly difficult in patients with severe scoliosis or who have undergone spinal fusion [75,76], and distribution of a drug is restricted to the central nervous system [18]. In many patients with SMA, veins are difficult to access, making intravenous administration challenging, especially if repeated injections are required, and oral administration, even though non-invasive, requires consideration of difficulty swallowing, which for some patients will require a percutaneous endoscopic gastrostomy tube [77].

Therapeutic approaches with different targets and routes of administration are currently in development [36,78]. As data are gathered, there should be three key considerations: comparative effectiveness of a treatment; identification of patient groups by trajectories or responsiveness to a given therapy; and the measurement treatment impact based on patient-relevant aspects of their disease. If successful, this means that in future patients may be able to choose the therapeutic approach that optimally reflects their needs in regard to target as well as administration.

4.6. Clinical trials

Participants showed a high willingness to engage in clinical trials, despite trial participation being burdensome and involving some risk. For many patients, participation in a clinical trial represents their only chance to receive a treatment or, if already on treatment, to discover whether another compound would have an even better effect. The frustration associated with lack of access was mirrored by those unable to take part in a trial. While participants appreciate the value of stabilization as an outcome, the keenness of treated patients to participate suggests individual patients are still in search of their individual optimal therapeutic benefit.

The willingness to engage in a placebo-controlled trial and accept associated burdens emphasizes the desperation for treatments. Regardless of the willingness, the recruitment of patients for future placebo-controlled clinical trials is likely to become increasingly difficult, particularly for treatment-naïve patients [30,36]. The use of placebo controls where established therapies are available is rare [79] even though placebo-controlled trials are considered acceptable [80,81], and it is ethically challenging, especially for severe conditions. A potential solution is considered in a recent study by Krol et al. (2020), with the use of active-controlled trials instead of placebo-controlled trials [82]. A recent Cochrane Library review describes nusinersen as the only therapy for SMA at the time of review publication for which there is moderate certainty of benefit, and new therapies should ideally either be compared with nusinersen or be evaluated as an add-on therapy [78].

Clinical trial designs should also be considered, given the impact of inclusion and exclusion criteria on approval and reimbursement. The design of the pediatric nusinersen trials meant placebo-controlled data were missing for the adult population, which comprises around a third of the global SMA population [51]. Many trials focus on early phases of the disease, as motor improvement or lack of decline are the most established ways to assess drug efficacy, and secondary effects such as scoliosis and contractures are less severe which simplifies assessments. However, therapies for individuals with a prolonged disease duration should also be sought to prevent disease progression, conserve motor function and improve quality of life [78]. The full picture of effectiveness includes specific motor scales and how they reflect activities of daily living [16,67], as well as measures of other patient-relevant aspects such as fatigue, fatigability, endurance, speaking/swallowing and respiration, scoliosis and contractures, sleep, pain and psychological problems [12–15,17,53].

Current clinical trial designs and their primary outcome measures assume an improvement through treatment and neglect the concept that a stabilization or a slowing of progression is also valuable for patients [53]. Chow and Huang (2020) present innovative trial design and analysis for drug development in rare diseases and highlight the concept of demonstrating 'not-ineffectiveness' rather than 'effectiveness' [80,83]. As disease progression in SMA is gradual, changes in function or stabilization – and thus identification of treatment responders – is difficult to demonstrate in a clinical trial setting, at least in part of the disease population. Yet stabilization is important and meaningful change is relative to functional ability, whereby small improvements in motor function could have an important impact on quality of life [53]. This should be considered when defining responders and non-responders to a treatment.

4.7. Study limitations and considerations on disease classification

EUPESMA-2019 includes the largest number of participants in a European SMA survey to date. Data were collected from participants of varying ages and geographical origins, both of which may have influenced study findings. Due to study design and sample size, some elements were not assessed, such as the relationship between geographical distribution and the natural history of SMA, or social aspects including limited computer access or lower registration levels to national patient associations. Also, we cannot exclude biases in expectations arising from the general outlook of participants, all of whom were proactive in their disease management by way of membership in a patient organization and completing a long questionnaire. This study did not focus on pre-symptomatic, early and newly diagnosed patients; these groups should be considered in future research, especially since they might have different expectations due to their lack of experience living with SMA. Finally, responses were participant reported and therefore aspects such as SMA type were not validated by clinicians. The data reflects the patient's perceptions and understanding exclusively; and it was processed objectively and comprehensively without assuming outliers, therefore some patients may have been given an inaccurate type classification at diagnosis or, also due to potential lack of patient records, did not pass on their diagnosis correctly in this survey.

4.8. Conclusion

EUPESMA-2019 showed that equal access for all who can benefit from a treatment is needed. Participants clearly indicate that stabilization of their clinical state is a benefit, they want to participate in clinical trials, and that alternative treatment options, combined or add-on therapeutic approaches focusing on different targets, are now expectations.

Patient perspectives and expectations need to be considered during SMA treatments development and discussions on treatment access. Stakeholders, including Patient Advocacy Groups, must work together to foster innovative solutions along the drug life cycle that incorporate new technologies involving artificial intelligence and 'big data' modelling of real-world data, to ensure drug development, including approval and reimbursement processes, is not restricted due to the rare disease status of SMA.

Above all, patients need safe and clinically effective therapies and evidence indicating which therapy is optimal for whom. From the patient perspective, stabilization and minor changes in functional ability can have meaningful impacts on their daily life. Our goal must be to gather evidence and drive research further to personalize medicine, so that each individual patient may have access to the therapy that provides individual optimal therapeutic benefit.

Declaration of Competing Interest

N.G. is a volunteer for SMA Europe and SMA Schweiz, mother of two children, one living with SMA, and advisor and lecturer for Biogen, Novartis, Novartis Gene Therapies (AveXis) and Roche. E.S. is a volunteer for SMA Europe, Initiative SMA and DGM, and mother of two grown up children, one living with SMA. C.S., L.K. and A.M. are paid staff at AFM Téléthon. M.-C.O. is a volunteer board member for SMA Europe, AFM Téléthon, and GENETHON, mother of twins, one living with SMA, and advisor for Biogen, Novartis and Novartis Gene Therapies (AveXis). M.dL. is a volunteer for SMA Europe and FundAME, mother of two children living with SMA, and advisor for Biogen, Novartis, Novartis Gene Therapies (AveXis), and Roche.

Acknowledgments

This work has been initiated and performed by SMA Europe with its member organizations AFM-Téléthon, Asociatia SMACARE, Children with SMA Ukraine, Deutsche Gesellschaft für Muskelkranke, Famiglie SMA, FSMA á Íslandi, Fundacja SMA, FundAME, Muskelsvindfonden,

Nätverket för spinal muskelatrofi, Prinses Beatrix Spierfonds, SMA Belgium, SMAci, SMA Family Foundation Russia, SMA Finland, SMA Schweiz, SMA Serbia, SMA UK, Stop SMA Macedonia, Vereniging Spierziekten Nederland. We acknowledge Vanessa Christie-Brown for logistical support and Markus Gusset for proof-reading the manuscript. Writing support was provided by Helen Smith of MediTech Media.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.nmd.2021.01.012.

Funding

Resources used to conduct this study were from SMA Europe member contributions exclusively.

References

[1] Verhaart IEC, Robertson A, Wilson IJ, Aartsma-Rus A, Cameron S, Jones CC, et al. Prevalence, incidence and carrier frequency of 5q-linked spinal muscular atrophy - a literature review. Orphanet J Rare Dis 2017;12:124. doi:10.1186/s13023-017-0671-8.

[2] Kolb SJ, Kissel JT. Spinal muscular atrophy. Neurol Clin 2015;33:831–46. doi:10.1016/j.ncl.2015.07.004.

[3] Sugarman EA, Nagan N, Zhu H, Akmaev VR, Zhou Z, Rohlfs EM, et al. Pan-ethnic carrier screening and prenatal diagnosis for spinal muscular atrophy: clinical laboratory analysis of >72,400 specimens. Eur J Hum Genet EJHG 2012;20:27–32. doi:10.1038/ejhg.2011.134.

[4] Lefebvre S, Burglen L, Reboullet S, Clermont O, Burlet P, Viollet L, et al. Identification and characterization of a spinal muscular atrophy-determining gene. Cell 1995;80:155–65. doi:10.1016/0092-8674(95)90460-3.

[5] Lefebvre S, Burlet P, Liu Q, Bertrandy S, Clermont O, Munnich A, et al. Correlation between severity and SMN protein level in spinal muscular atrophy. Nat Genet 1997;16:265–9. doi:10.1038/ng0797-265.

[6] Lorson CL, Hahnen E, Androphy EJ, Wirth B. A single nucleotide in the SMN gene regulates splicing and is responsible for spinal muscular atrophy. PNAS USA 1999;96:6307–11. doi:10.1073/pnas.96.11.6307.

[7] Mercuri E, Lucibello S, Perulli M, Coratti G, de Sanctis R, Pera MC, et al. Longitudinal natural history of type I spinal muscular atrophy: a critical review. Orphanet J Rare Dis 2020;15:84. doi:10.1186/s13023-020-01356-1.

[8] Mercuri E, Kirschner J, Baranello G, Servais L, Goemans N, Pera M, et al. Clinical studies of RG7916 in patients with spinal muscular atrophy: SUNFISH part 1 study update. Neuromuscul Disord NMD 2017;27:S209. doi:10.1016/j.nmd.2017.06.415.

[9] Mercuri E, Finkel RS, Muntoni F, Wirth B, Montes J, Main M, et al. Diagnosis and management of spinal muscular atrophy: Part 1: Recommendations for diagnosis, rehabilitation, orthopedic and nutritional care. Neuromuscul Disord NMD 2018;28:103–15. doi:10.1016/j.nmd.2017.11.005.

[10] Ho HM, Tseng YH, Hsin YM, Chou FH, Lin WT. Living with illness and self-transcendence: the lived experience of patients with spinal muscular atrophy. J Adv Nurs 2016;72:2695–705. doi:10.1111/jan.13042.

[11] Mongiovi P, Dilek N, Garland C, Hunter M, Kissel JT, Luebbe E, et al. Patient reported impact of symptoms in spinal muscular atrophy (PRISM-SMA). Neurology 2018;91:e1206 -e14. doi:10.1212/WNL.0000000000006241.

[12] Stam M, Wadman RI, Bartels B, Leeuw M, Westeneng HJ, Wijngaarde CA, et al. A continuous repetitive task to detect fatigability in spinal muscular atrophy. Orphanet J Rare Dis 2018;13:160. doi:10.1186/s13023-018-0904-5.

[13] Wijngaarde CA, Veldhoen ES, van Eijk RPA, Stam M, Otto LAM, Asselman FL, et al. Natural history of lung function in spinal muscular atrophy. Orphanet J Rare Dis 2020;15:88. doi:10.1186/s13023-020-01367-y.

[14] Fujak A, Raab W, Schuh A, Richter S, Forst R, Forst J. Natural course of scoliosis in proximal spinal muscular atrophy type II and IIIa: descriptive clinical study with retrospective data collection of 126 patients. BMC Musculoskelet Disord 2013;14:283. doi:10.1186/1471-2474-14-283.

[15] Prior TW, Leach ME, Finanger E. Spinal Muscular Atrophy; 1993. In: Adam M P, et al ed. GeneReviews®. Seattle (WA).

[16] Messina S, Frongia AL, Antonaci L, Pera MC, Coratti G, Pane M, et al. A critical review of patient and parent caregiver oriented tools to assess health-related quality of life, activity of daily living and caregiver burden in spinal muscular atrophy. Neuromuscul Disord NMD 2019;29:940–50. doi:10.1016/j.nmd.2019.10.001.

[17] Qian Y, McGraw S, Henne J, Jarecki J, Hobby K, Yeh WS. Understanding the experiences and needs of individuals with spinal muscular atrophy and their parents: a qualitative study. BMC Neurol 2015;15:217. doi:10.1186/s12883-015-0473-3.

[18] Farrar MA, Teoh HL, Carey KA, Cairns A, Forbes R, Herbert K, et al. Nusinersen for SMA: expanded access programme. J Neurol Neurosurg Psychiatry 2018;89:937–42. doi:10.1136/jnnp-2017-317412.

[19] Lopez-Bastida J, Pena-Longobardo LM, Aranda-Reneo I, Tizzano E, Sefton M, Oliva-Moreno J. Social/economic costs and health-related quality of life in patients with spinal muscular atrophy (SMA) in Spain. Orphanet J Rare Dis 2017;12:141. doi:10.1186/s13023-017-0695-0.

[20] Armstrong EP, Malone DC, Yeh WS, Dahl GJ, Lee RL, Sicignano N. The economic burden of spinal muscular atrophy. J Med Econ 2016;19:822–6. doi:10.1080/13696998.2016.1198355.

[21] Gillingwater TH. Counting the cost of spinal muscular atrophy. J Med Econ 2016;19:827–8. doi:10.1080/13696998.2016.1202833.

[22] Klug C, Schreiber-Katz O, Thiele S, Schorling E, Zowe J, Reilich P, et al. Disease burden of spinal muscular atrophy in Germany. Orphanet J Rare Dis 2016;11:58. doi:10.1186/s13023-016-0424-0.

[23] Landfeldt E, Edstrom J, Sejersen T, Tulinius M, Lochmuller H, Kirschner J. Quality of life of patients with spinal muscular atrophy: a systematic review. Eur J Paediatr Neurol EJPN Off J Eur Paediatr Neurol Soc 2019;23:347–56. doi:10.1016/j.ejpn.2019.03.004.

[24] Biogen Inc. SPINRAZA® (nusinersen) US prescribing information. Dec 2016 [cited 2020 29 June]; Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/209531lbl.pdf.

[25] Biogen Inc. SPINRAZA® (nusinersen) EMA prescribing information. Dec 2017 [cited 2020 29 June]; Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/004312/WC500229704.pdf.

[26] AveXis Inc. ZOLGENSMA® (onasemnogene abeparvovec-xioi) US prescribing information. May 2019 [cited 2020 29 June]; Available from: https://www.fda.gov/media/126109/download.

[27] European Medicines Agency. Zolgensma. May 2020 [cited 2020 30 June]; Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/zolgensma.

[28] Hoy S. Onasemnogene abeparvovec: first global approval. Drugs 2019;79:1255–62. doi:10.1007/s40265-019-01162-5.

[29] Ratni H, Ebeling M, Baird J, Bendels S, Bylund J, Chen KS, et al. Discovery of risdiplam, a selective survival of motor neuron-2 (SMN2) gene splicing modifier for the treatment of spinal muscular atrophy (SMA). J Med Chem 2018;61:6501–17. doi:10.1021/acs.jmedchem.8b00741.

[30] Schorling DC, Pechmann A, Kirschner J. advances in treatment of spinal muscular atrophy - new phenotypes, new challenges, new implications for care. J Neuromuscul Dis 2020;7:1–13. doi:10.3233/JND-190424.

[31] Wang CH, Finkel RS, Bertini ES, Schroth M, Simonds A, Wong B, et al. Consensus statement for standard of care in spinal muscular atrophy. J Child Neurol 2007;22:1027–49. doi:10.1177/0883073807305788.

[32] Finkel RS, Mercuri E, Meyer OH, Simonds AK, Schroth MK, Graham RJ, et al. Diagnosis and management of spinal muscular atrophy: part 2: pulmonary and acute care; medications, supplements and immunizations; other organ systems; and ethics. Neuromuscul Disord NMD 2018;28:197–207. doi:10.1016/j.nmd.2017.11.004.
[33] Wang CH, Lunn MR. Spinal muscular atrophy: advances in research and consensus on care of patients. Curr Treat Opt Neurol 2008;10:420–8. doi:10.1007/s11940-008-0044-7.
[34] Gidaro T, Servais L. Nusinersen treatment of spinal muscular atrophy: current knowledge and existing gaps. Dev Med Child Neurol 2019;61:19–24. doi:10.1111/dmcn.14027.
[35] Rouault F, Christie-Brown V, Broekgaarden R, Gusset N, Henderson D, Marczuk P, et al. Disease impact on general well-being and therapeutic expectations of European Type II and Type III spinal muscular atrophy patients. Neuromuscul Disord NMD 2017;27:428–38. doi:10.1016/j.nmd.2017.01.018.
[36] Groen EJN, Talbot K, Gillingwater TH. Advances in therapy for spinal muscular atrophy: promises and challenges. Nat Rev Neurol 2018;14:214–24. doi:10.1038/nrneurol.2018.4.
[37] Chiriboga CA, Swoboda KJ, Darras BT, Iannaccone ST, Montes J, De Vivo DC, et al. Results from a phase 1 study of nusinersen (ISIS-SMNRx) in children with spinal muscular atrophy. Neurology 2016;86:890–7. doi:10.1212/WNL.0000000000002445.
[38] Finkel RS, Chiriboga CA, Vajsar J, Day JW, Montes J, De Vivo DC, et al. Treatment of infantile-onset spinal muscular atrophy with nusinersen: a phase 2, open-label, dose-escalation study. Lancet (London, England) 2016;388:3017–26 S0140-6736(16)31408-8.
[39] Finkel RS, Mercuri E, Darras BT, Connolly AM, Kuntz NL, Kirschner J, et al. Nusinersen versus sham control in infantile-onset spinal muscular atrophy. N Engl J Med 2017;377:1723–32. doi:10.1056/NEJMoa1702752.
[40] Hagenacker T, Wurster CD, Günther R, Schreiber-Katz O, Osmanovic A, Petri S, et al. Nusinersen in adults with 5q spinal muscular atrophy: a non-interventional, multicentre, observational cohort study. Lancet Neurol 2020;19:317–25. doi:10.1016/S1474-4422(20)30037-5.
[41] Mercuri E, Barisic N, Boespflug-Tanguy O, Day JW, Deconinck N, Kostera-Pruszczyk A, et al. SUNFISH part 2: efficacy and safety of risdiplam (RG7916) in patients with Type 2 or non-ambulant Type 3 spinal muscular atrophy (SMA). In: Presented at the SMA Europe; 2020. 2020.
[42] Wurster CD, Ludolph AC. Antisense oligonucleotides in neurological disorders. Ther Adv Neurol Disord 2018;11 1756286418776932. doi:10.1177/1756286418776932.
[43] Zingariello CD, Brandsema J, Drum E, Henderson AA, Dubow S, Glanzman AM, et al. A multidisciplinary approach to dosing nusinersen for spinal muscular atrophy. Neurol Clin Pract 2019;9:424–32. doi:10.1212/CPJ.0000000000000718.
[44] Mousa MA, Aria DJ, Schaefer CM, Kaye RD, Abruzzo TA, Bernes SM, et al. A comprehensive institutional overview of intrathecal nusinersen injections for spinal muscular atrophy. Pediatr Radiol 2018;48:1797–805. doi:10.1007/s00247-018-4206-9.
[45] Hensel N, Kubinski S, Claus P. The need for SMN-independent treatments of spinal muscular atrophy (SMA) to complement SMN-enhancing drugs. Front Neurol 2020;11:45. doi:10.3389/fneur.2020.00045.
[46] Feng Z, Ling KK, Zhao X, Zhou C, Karp G, Welch EM, et al. Pharmacologically induced mouse model of adult spinal muscular atrophy to evaluate effectiveness of therapeutics after disease onset. Hum Mol Genet 2016;25:964–75. doi:10.1093/hmg/ddv629.
[47] Long KK, O'Shea KM, Khairallah RJ, Howell K, Paushkin S, Chen KS, et al. Specific inhibition of myostatin activation is beneficial in mouse models of SMA therapy. Hum Mol Genet 2019;28:1076–89. doi:10.1093/hmg/ddy382.
[48] Zhou H, Meng J, Malerba A, Catapano F, Sintusek P, Jarmin S, et al. Myostatin inhibition in combination with antisense oligonucleotide therapy improves outcomes in spinal muscular atrophy. J Cachexia Sarcopenia Muscle 2020:768–82. doi:10.1002/jcsm.12542.
[49] Warner K, See W, Haerry D, Klingmann I, Hunter A, May M. EUPATI guidance for patient involvement in medicines research and development (R&D); guidance for pharmaceutical industry-led medicines R&D. Front Med (Lausanne) 2018;5:270. doi:10.3389/fmed.2018.00270.
[50] Gaasterland CMW, van der Weide MCJ, du Prie-Olthof MJ, Donk M, Kaatee MM, Kaczmarek R, et al. The patient's view on rare disease trial design - a qualitative study. Orphanet J Rare Dis 2019;14:31. doi:10.1186/s13023-019-1002-z.
[51] Wan HWY, Carey KA, D'Silva A, Kasparian NA, Farrar MA. Getting ready for the adult world": how adults with spinal muscular atrophy perceive and experience healthcare, transition and well-being. Orphanet J Rare Dis 2019;14:74. doi:10.1186/s13023-019-1052-2.
[52] Sacristan JA, Aguaron A, Avendano-Sola C, Garrido P, Carrion J, Gutierrez A, et al. Patient involvement in clinical research: why, when, and how. Patient Prefer Adher 2016;10:631–40. doi:10.2147/PPA.S104259.
[53] McGraw S, Qian Y, Henne J, Jarecki J, Hobby K, Yeh WS. A qualitative study of perceptions of meaningful change in spinal muscular atrophy. BMC Neurol 2017;17:68. doi:10.1186/s12883-017-0853-y.
[54] Verhaart IEC, Robertson A, Leary R, McMacken G, Konig K, Kirschner J, et al. A multi-source approach to determine SMA incidence and research ready population. J Neurol 2017;264:1465–73. doi:10.1007/s00415-017-8549-1.
[55] Mercuri E, Finkel R, Montes J, Mazzone ES, Sormani MP, Main M, et al. Patterns of disease progression in type 2 and 3 SMA: implications for clinical trials. Neuromuscul Disord NMD 2016;26:126–31. doi:10.1016/j.nmd.2015.10.006.
[56] Finkel RS, Castro D, Farrar MA, Tulinius M, Krosschell KJ, Saito K, et al. Interim report on the safety and efficacy of longer-term treatment with nusinersen in infantile-onset spinal muscular atrophy (SMA): Updated results from the SHINE study. In: Communication presented at American Academy of Neurology 2019 – 71st Annual Meeting; 2019. May 4-10.
[57] Wadman RI, Wijngaarde CA, Stam M, Bartels B, Otto LAM, Lemmink HH, et al. Muscle strength and motor function throughout life in a cross-sectional cohort of 180 patients with spinal muscular atrophy types 1c-4. Eur J Neurol Off J Eur Fed Neurol Soc 2018;25:512–18. doi:10.1111/ene.13534.
[58] Inc B, *Landmark NURTURE study of infants with spinal muscular atrophy (sMA) treated pre-symptomatically with SPINRAZA® (nusinersen) published in Neuromuscular Disorders*. 2019.
[59] Tizzano EF, Finkel RS. Spinal muscular atrophy: A changing phenotype beyond the clinical trials. Neuromuscul Disord NMD 2017;27:883–9. doi:10.1016/j.nmd.2017.05.011.
[60] Radu M, Radu G, Condurache A. Lorin purcarea V. The influence of digital media on the success of a health care unit. J Med Life 2018;11:254–6. doi:10.25122/jml-2018-0064.
[61] King NMP, Bishop CE. New treatments for serious conditions: ethical implications. Gene Ther 2017;24:534–8. doi:10.1038/gt.2017.32.
[62] Mendell JR. Single-dose gene-replacement therapy for spinal muscular atrophy. N Engl J Med 2017;377:1713–22. doi:10.1056/NEJMoa1706198.
[63] Haahr A, Kirkevold M, Hall EO, Ostergaard K. Living with advanced Parkinson's disease: a constant struggle with unpredictability. J Adv Nurs 2011;67:408–17. doi:10.1111/j.1365-2648.2010.05459.x.
[64] Ahn S, Lee J, Chu SH, Sohn YH. Uncertainty and depression in people with Parkinson's disease: a cross-sectional study. Nurs Health Sci 2017;19:220–7. doi:10.1111/nhs.12332.
[65] Bell M, Biesecker BB, Bodurtha J, Peay HL. Uncertainty, hope, and coping efficacy among mothers of children with Duchenne/Becker muscular dystrophy. Clin Genet 2019;95:677–83. doi:10.1111/cge.13528.
[66] Keramat Kar M, Whitehead L, Smith CM. Characteristics and correlates of coping with multiple sclerosis: a systematic review. Disabil Rehabil 2019;41:250–64. doi:10.1080/09638288.2017.1387295.
[67] Giovannetti AM, Brambilla L, Torri Clerici V, Antozzi C, Mantegazza R, Cerniauskaite M, et al. Difficulties in adjustment to multiple sclerosis: vulnerability and unpredictability of illness in the

foreground. Disabil Rehabil 2017;39:897–903. doi:10.3109/09638288.2016.1170212.

[68] NICE. NICE would welcome further discussions about access to spinal muscular atrophy drug nusinersen. 2018 [cited 2020 29 June]; Available from: https://www.nice.org.uk/news/article/nice-would-welcome-further-discussions-about-access-to-spinal-muscular-atrophy-drug-nusinersen.

[69] Young KE, Soussi I, Hemels M, Toumi M. A comparative study of orphan drug prices in Europe. J Mark Access Health Policy 2017;5:1297886. doi:10.1080/20016689.2017.1297886.

[70] Azzopardi-Muscat N, Baeten R, Clemens T, Habicht T, Keshimaki I, Kowalska-Bobko I, et al. The role of the 2011 Patients' rights in cross-border health care directive in shaping seven national health systems: looking beyond patient mobility. Health Policy 2018;122:279–83. doi:10.1016/j.healthpol.2017.12.010.

[71] Farrar MA, Park SB, Vucic S, Carey KA, Turner BJ, Gillingwater TH, et al. Emerging therapies and challenges in spinal muscular atrophy. Ann Neurol 2017;81:355–68. doi:10.1002/ana.24864.

[72] Hamilton G, Gillingwater TH. Spinal muscular atrophy: going beyond the motor neuron. Trends Mol Med 2013;19:40–50. doi:10.1016/j.molmed.2012.11.002.

[73] Nash LA, Burns JK, Chardon JW, Kothary R, Parks RJ. Spinal muscular atrophy: more than a disease of motor neurons? Curr Mol Med 2016;16:779–92. doi:10.2174/1566524016666161128113338.

[74] Hua Y, Sahashi K, Rigo F, Hung G, Horev G, Bennett CF, et al. Peripheral SMN restoration is essential for long-term rescue of a severe spinal muscular atrophy mouse model. Nature 2011;478:123–6. doi:10.1038/nature10485.

[75] Stolte B, Totzeck A, Kizina K, Bolz S, Pietruck L, Monninghoff C, et al. Feasibility and safety of intrathecal treatment with nusinersen in adult patients with spinal muscular atrophy. Ther Adv Neurol Disord 2018;11 1756286418803246. doi:10.1177/1756286418803246.

[76] Wurster CD, Winter B, Wollinsky K, Ludolph A, Uzelac Z, Witzel S, et al. Intrathecal administration of nusinersen in adolescent and adult SMA Type 2 and 3 patients. J Neurol 2019;266:183–94. doi:10.1007/s00415-018-9124-0.

[77] Arnold WD, Kassar D, Kissel JT. Spinal muscular atrophy: diagnosis and management in a new therapeutic era. Muscle Nerve 2015;51:157–67. doi:10.1002/mus.24497.

[78] Wadman RI, van der Pol WL, Bosboom WM, Asselman FL, van den Berg LH, Iannaccone ST, et al. Drug treatment for spinal muscular atrophy types II and III. The cochrane database of systematic reviews 2020;1:CD006282. doi:10.1002/14651858.CD006282.pub5.

[79] Batra S, Howick J. Empirical evidence against placebo controls. J Med Ethics 2017. doi:10.1136/medethics-2016-103970.

[80] Chow SC, Huang Z. Innovative design and analysis for rare disease drug development. J Biopharm Stat 2020;30:537–49. doi:10.1080/10543406.2020.1726371.

[81] World Medical A. World medical association declaration of Helsinki. Ethical principles for medical research involving human subjects. JAMA 2013;310:2191–4. doi:10.1001/jama.2013.281053.

[82] Krol FJ, Hagin M, Vieta E, Harazi R, Lotan A, Strous RD, et al. Placebo-to be or not to be? Are there really alternatives to placebo-controlled trials? Eur Neuropsychopharmacol 2020;32:1–11. doi:10.1016/j.euroneuro.2019.12.117.

[83] Chow SC, Huang Z. Demonstrating effectiveness or demonstrating not ineffectiveness - A potential solution for rare disease drug product development? J Biopharm Stat 2019;29:897–907. doi:10.1080/10543406.2019.1657137.