# Ethical Perspectives on Treatment Options with Spinal Muscular Atrophy Patients

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Since 2016, 3 innovative therapies for spinal muscular atrophy (SMA) have changed the face of the disease. Although these therapies often result in remarkable improvements in infants and children, benefits in adults are modest and treatment is not curative. Concerns have been raised about the enormous costs of these medications, the ultimate burden to taxpayers, and the costs to society of withholding treatments and sacrificing or disadvantaging some individuals. Physicians are best positioned to serve our patients by carefully considering the costs, benefits, implications for quality of life (QOL), and the interplay of these factors within the framework of core ethical principles that guide clinical care.

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The past 5 years have been a watershed for the treatment of SMA. In August 2020, risdiplam (Evrysdi) was approved by the Federal Drug Administration (FDA) as the third disease-modifying treatment for SMA and only the second for patients older than 2 years.[1] In March 2021, it was approved by the European Medicines Agency (EMA) for treating SMA types 1, 2, and 3 with up to 4 copies of the Survival Motor Neuron 2 (*SMN2*) gene (Table 1). Prior to 2020, the antisense oligonucleotide (ASO) nusinersen (Spinraza) was FDA-approved in December 2016 and EMA-approved in May 2017 for SMA patients of all ages. Gene replacement therapy onasemnogene abeparvovec-xioi (Zolgensma) was FDA-approved in May 2019 for SMA patients younger than 2 years[2,3] and EMA-approved in June 2020 for all patients with 3 or fewer *SMN2* copies and weighing ≤21kg. These effective therapies are not curative but prolong lifespan in infants and children, allow motor milestones to be attained, and allow better QOL.[4–6] In adults, there are questions regarding efficacy when the motor neuron pool has been significantly diminished, and benefits of treatment are not clearly measurable. All drugs have inherent risks, and these innovative therapies are enormously expensive, with nusinersen costing US $750,000 in the 1st year and US $375,000 subsequently, onasemnogene abeparvovec-xioi costing US $2.125 million and risdiplam costing US $340,000 per year once a patient reaches 44lbs.[7–9] Implementation of newborn screening programs across many states of the United States and Europe has accelerated diagnosis and treatment of SMA and brought up pressing questions on how best to individualize patient care. As physicians, we best discharge our duty to act in our patients' best interests by making a careful study of the costs, benefits, implications for QOL, and the interplay of these factors within the framework of ethical principles that guide clinical care.

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## Ethical Principles

Physicians have a duty to make sure that our patients have the right information to make decisions on their medical care. Children have limited capacity to make decisions and lack legal authority; therefore, their parents or legal guardians should have sufficient knowledge to act in their best interests as surrogate decision-makers. Ethical principles of autonomy, beneficence, and nonmaleficence[10] are often viewed through the lens of the individual physician providing care to their patients, whereas the ethical principle of justice is usually viewed in medicine through the lens of society and centers around equitable allocation of scarce resources. Although decisions on health care resources are frequently made by government agencies, physicians can and should play a role in such decisions. This has immediate relevance to the treatment of SMA in view of the enormous cost of these medications, ultimate burden of such costs to taxpayers, and costs to society of withholding treatments and sacrificing or disadvantaging some individuals. In this paper, we address primarily the ethics of individual patient care, but also briefly consider broader societal ethical implications.

## Biology of SMA

SMA is a neuromuscular disease driven by motor neuron death. The carrier frequency of SMA is approximately 1/54, and disease incidence is approximately 1/11,000.[11] It is caused by biallelic loss of function mutations in the *SMN1* gene and scarcity of SMN protein.[12] In humans, a paralogue gene, *SMN2*, exists, which differs from *SMN1* by a small number of nucleotides, the most important being a c.840 C>T transition in exon 7 (Fig). This change modifies splicing enhancer/silencer sites in exon 7, resulting in the aberrant splicing out of exon 7 in most transcripts, and the production of mostly truncated and nonfunctional SMN protein. Fewer *SMN2* copies are associated with the most severe phenotypes (SMA types 0 and 1), which have onset of disease prenatally and in infancy.[12] Incrementally, more copies of *SMN2* result in intermediate (SMA type 2) and milder (SMA types 3 and 4) phenotypes, with disease onset in childhood and adulthood. Innovative therapies have focused on increasing the production of functional full-length SMN protein, either by rectifying the aberrant splicing out of exon 7 in *SMN2* (nusinersen and risdiplam) or by replacing the defective *SMN1* gene (onasemnogene abeparvovec-xioi). Nusinersen is given intrathecally every 4 months after 4 loading doses over 2 months, risdiplam is given orally every day, and onasemnogene abeparvovec-xioi is given intravenously as one dose (see Fig, Table 1).

## Benefits and Risks of Nusinersen to Individuals

Nusinersen is intrathecally administered and augments SMN protein expression in the central nervous system. Remarkable prolongation of life and motor improvements have been seen in phase 3 clinical trials conducted in infants with SMA (see Table 1), but observational cohort studies in adults with SMA show only modest benefit characterized by stabilization or minimal improvements in motor function and gait stability compared to historical controls.[13–16] Nusinersen has a good safety profile and has been FDA- and EMA-approved with few precautions (Table 2), but lumbar punctures, albeit burdensome even in children due to scoliosis and sometimes the need for anesthesia, are more challenging in adults due to complications of long-term disease, such as scoliosis, fused spines, and other coexisting diseases.

Like all ASOs, nusinersen is unable to cross the mature blood–brain barrier. Site of action of SMN protein augmentation gains importance when considering the ubiquitous expression of SMN protein in every tissue and its important housekeeping functions. Animal models and autopsies suggest that very low SMN protein expression can cause dysfunction in most peripheral organs, although it may not always be clinically manifest in humans.[17–23] One study in SMA mice suggested that SMN protein expression in peripheral tissues could affect motor neuron survival and lifespan.[22] Because nusinersen acts only on the central nervous system, infants and children treated with nusinersen are surviving with low levels of SMN protein in peripheral organs. Implications of lifelong treatment under these conditions are unknown.[24]

Parents may not be aware of these nuances and, therefore, are unable to critically appraise original medical and scientific literature. Even among SMA experts, there is lack of consensus as to whether SMA is multisystemic or a pure motor neuron disease.[22] Should SMN-augmenting therapies that target only the central nervous system result in potential extraneuronal phenotypes, then a multidisciplinary team approach to prevent and treat such effects is important.[24]

In adults, observation studies show stabilization or 2- to 3-point improvement in motor assays, when a clinically meaningful effect is widely thought to be 3 or more points on the Hammersmith Functional Motor Scale Expanded (HFMSE).[13–16] Beneficial effects on energy and endurance are poorly quantified by available patient-reported outcome scales.[16] Patient selection is important, because HFMSE improvements are more evident in high-functioning adults with no respiratory difficulties or scoliosis.[16] Longer duration of treatment may increase the effect,[16,25] and optimization by dose and dosing frequency may be required to see beneficial effects in adults.[16]

**TABLE 1. Summary of 3 Innovative Therapies for Spinal Muscular Atrophy**

| Drug | MOA | Dosage | FDA Approval and Indications | EMA Approval and Indications | Annual Cost, USD | Relevant Clinical Trials |
|---|---|---|---|---|---|---|
| Nusinersen | ASO that modulates *SMN2* splicing | Intrathecal 12mg × 4 loading doses/2 mo then every 4 mo | December 2016 All SMA patients, regardless of age or type | May 2017 All SMA patients, regardless of age or type | $750,000 the 1st year then $375,000 per year | ENDEAR (NCT02193074): Improved survival and motor function in symptomatic early onset SMA type 1 infants.[6] NURTURE (NCT02386553): Improved survival and motor function in presymptomatic SMA infants with 2 or 3 copies of *SMN2*.[48,50] CHERISH (NCT02292537): Improved motor function in children with later onset SMA.[25] |
| Onasemnogene abeparvovec-xioi | AAV9 that carries replacement *SMN1* gene | Intravenous 1.1 × 10^14vg/kg of body weight, given one time | May 2019 SMA patients <2 yr old | June 2020 All SMA patients with ≤3 *SMN2* copies and ≤21 kg | $2,125,000 one time | START (NCT02122952) and STR1VE (NCT03306277), USA and EU: Improved survival and motor function in symptomatic early onset SMA type 1 infants.[4,27,30] SPR1NT (NCT03505099): Improved survival and motor function in presymptomatic SMA infants with 2 or 3 copies of *SMN2*.[49] |
| Risdiplam | Small molecule drug that modulates *SMN2* splicing | Oral 0.2mg/kg for <2 yr of age; 0.25mg/kg for weight < 20kg and age ≥ 2 yr; 5mg for age ≥ 2 yr with weight ≥ 20kg | August 2020 All SMA patients with age > 2 mo | March 2021 SMA Types 1–3 with up to 4 copies of the *SMN2* gene | $100,000–$340,000 per year | FIREFISH (NCT02913482): Improved survival and motor function in symptomatic SMA type 1 infants vs historical controls.[5] RAINBOWFISH[a] (NCT03779334): Improved survival and motor function in presymptomatic SMA infants with 2 or 3 copies of *SMN2*. SUNFISH (NCT02908685): Improved motor function in children and adults with SMA type 2 and ambulant or nonambulant type 3.[39] |

[a]Source: Roche, https://www.roche.com/media/releases/med-cor-2021-06-11.htm.

AAV = adeno-associated virus; ASO = antisense oligonucleotide; EMA = European Medicines Agency; FDA = US Food and Drug Agency; MOA = mechanism of action; SMA = Spinal Muscular Atrophy; SMN = survival motor neuron; USD = US dollars; VG = vector genomes.

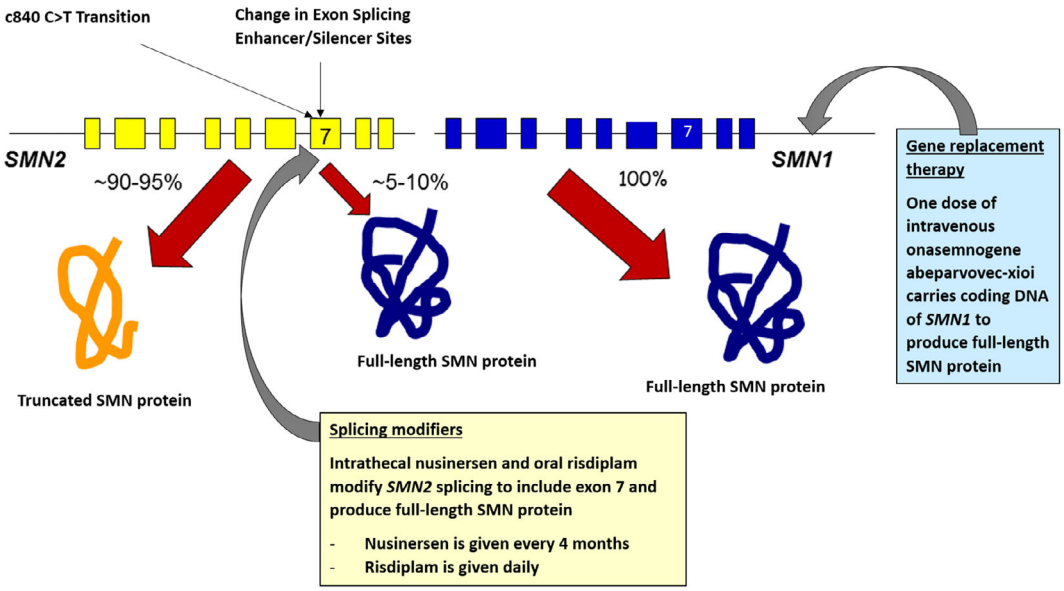


**FIGURE: Biology of spinal muscular atrophy and innovative therapies. Schematic of *SMN1/2* genes and actions of SMN protein-augmenting therapies. Patients with spinal muscular atrophy have exon 7 deletions or mutations in both copies of *SMN1*. In *SMN2*, a C-to-T transition in exon 7 leads to production of a mostly truncated and nonfunctional SMN protein with a small proportion of functional full-length SMN protein. The splicing modifiers (left) intrathecal nusinersen and oral risdiplam modulate *SMN2* exon 7 splicing to increase the production of full-length SMN protein. Gene replacement therapy (right), with intravenous onasemnogene abeparvovec-xioi, carries a constitutively expressed *SMN1* gene, which produces full-length SMN protein.**

Higher doses of nusinersen are currently being studied in children and adults with SMA.[26]

Adults with SMA may not be aware that clinical trials for nusinersen have not been conducted in adults, benefits for adults are modest, or current FDA-approved dosage of nusinersen is the same in adults and children (see Table 1). Cerebrospinal fluid volume increases from 30 to 50ml in neonates to >120ml in adults, and thus larger doses may be required and/or be more effective in older children and adults. Adults may not understand what FDA approval means. They might be misled into thinking that a drug approved by the FDA for all patients with SMA must be effective for all patients with that diagnosis and misperceive an approved drug for one that is effective rather than one that is safe.

## Benefits and Risks of Onasemnogene Abeparvovec-Xioi to Individuals

A one-time intravenous dose of onasemnogene abeparvovec-xioi prolongs lifespan and motor function in infants and children,[4,27] with younger and stronger patients deriving most benefit (see Table 1).[28] Gene therapy has not been studied in adults. The adeno-associated virus (AAV) vector is relatively safe, as most infused vector genomes are deposited as episomes. Monitoring is recommended for side effects like thrombocytopenia and troponin I elevation, which may occur within days to a few weeks, with raised liver enzymes ameliorated by steroids,[4] and rare complications like thrombotic microangiopathy may be fatal (see Table 2).[29] However, the systemic administration of this drug may offer advantages over nusinersen administered intrathecally as discussed earlier.

Physicians should be aware of nuances regarding the use of AAV vectors and gene therapies. Onasemnogene abeparvovec-xioi cannot be given to patients with high AAV9 antibody titers or more than once because the body develops an immune response to the virus (see Table 2). Antibodies may limit patient suitability. Albeit a rare occurrence, infants may be born with high passive AAV antibody titers (>1:50), but older patients do have a greater risk of high AAV9 antibody titers.[4] Despite good short-term durability thus far, long-term durability and real-world safety of this treatment have not been proven.[30] Vector DNA does not integrate into host DNA, so long-term expression depends on AAV9 transduction efficacy, and loss of transduced cells by division and death. Because the highest transduction efficiency of motor neurons in animal models is only 60 to 70%,[31,32] untransduced motor neurons may benefit from ongoing SMN augmentation. Glial cells, which give neurotrophic support to motor neurons, and cells in peripheral organs can divide and dilute episomes. In animals, AAV can be genotoxic and increase risk of hepatocellular cancer.[33,34] There are no head-to-head comparison studies between onasemnogene abeparvovec-xioi and nusinersen or risdiplam. Therefore, physicians and families

**TABLE 2. Recommended Precautions for 3 Treatments for Spinal Muscular Atrophy**

| Drug | FDA Precautions | EMA Precautions |
|---|---|---|
| Nusinersen | Monitor platelet count, INR, PT/PTT, and quantitative spot urine protein at baseline and prior to each maintenance. | There is a risk of adverse reactions occurring as part of the lumbar puncture procedure.<br>If clinically indicated, platelet and coagulation laboratory testing is recommended prior to administration.<br>If clinically indicated, urine protein testing is recommended. For persistent elevated urinary protein, further evaluation should be considered. |
| Onasemnogene abeparvovec-xioi | Perform baseline testing for the presence of anti-AAV9 antibodies.<br>Prior to infusion, assess liver function of all patients by clinical examination and laboratory testing.<br>Administer systemic corticosteroid to all patients before and after infusion.<br>Continue to monitor liver function for at least 3 mo after infusion.<br>Monitor platelet counts before infusion, and weekly for the 1st mo and then every other week for the 2nd and 3rd mo until platelet counts return to baseline.<br>If clinical signs, symptoms, and/or laboratory findings of thrombotic microangiopathy occur, consult a pediatric hematologist and/or pediatric nephrologist immediately to manage as clinically indicated.<br>Monitor troponin-I before infusion, and weekly for the 1st mo and then monthly for the 2nd and 3rd mo until troponin-I level returns to baseline. | Patients should be tested for the presence of AAV9 antibodies prior to infusion. Retesting may be performed if AAV9 antibody titers are reported as >1:50.<br>Immune-mediated hepatotoxicity may require adjustment of the immunomodulatory regimen, including longer duration, increased dose, or prolongation of the corticosteroid taper.<br>Prior to infusion, liver function of all patients should be assessed by clinical examination and laboratory testing.<br>Platelet counts should be obtained before infusion and should be closely monitored in the week following infusion and on a regular basis afterward, weekly for the 1st mo and every other week for the 2nd and 3rd mo until platelet counts return to baseline.<br>In case of thrombocytopenia, further evaluation including diagnostic testing for hemolytic anemia and renal dysfunction should be undertaken. If patients show clinical signs, symptoms, or laboratory findings consistent with thrombotic microangiopathy, a specialist should be consulted immediately to manage as clinically indicated.<br>Troponin-I levels should be obtained before infusion and monitored for at least 3 mo or until levels return to within normal reference range for SMA patients. |
| Risdiplam | Avoid use in patients with impaired hepatic function.<br>Pregnancy testing is recommended for females of reproductive potential prior to initiating.<br>Advise female patients of reproductive potential to use effective contraception during treatment and for at least 1 mo after her last dose.<br>Male patients may consider sperm preservation prior to treatment. | Embryo–fetal toxicity has been observed in animal studies. Patients of reproductive potential should be informed of the risks and must use highly effective contraception during treatment and until at least 1 mo after the last dose in female patients, and 4 mo after the last dose in male patients.<br>The pregnancy status of female patients of reproductive potential should be verified prior to initiating therapy.<br>Prior to initiating treatment, fertility preservation strategies should be discussed with male patients of reproductive potential. |

AAV = adeno-associated virus; EMA = European Medicines Agency; FDA = US Food and Drug Administration; INR = international normalized ratio; PT = prothrombin time; PTT = partial thromboplastin time; SMA = spinal muscular atrophy.

must be careful and informed when choosing between these drugs for the child younger than 2 years (FDA) or weighing ≤21kg (EMA).

Onasemnogene abeparvovec-xioi has the reputation of being the "most expensive drug in the world."[35] It is marketed as a "one-time" treatment by Novartis and is

regarded as such by insurers. Parents and patients may misinterpret the use of onasemnogene abeparvovec-xioi as a one-time therapy to mean that it is a "once and done" cure for SMA. However, response is variable, and symptomatic patients do not regain normal motor function.[4] Normal levels of SMN may not be achieved in all surviving motor neurons, and the size of the available motor neuron pool and degree of successful transduction may affect drug efficacy. Retrospective studies of patients who have been on both onasemnogene abeparvovec-xioi and nusinersen therapies suggest that combination therapy may be an option if infants do not do as well as expected on monotherapy.[36] In practice, this would depend on clinical trial results and the approval from third-party payers in the United States. A clinical trial has begun to evaluate the effects of nusinersen on patients who have received onasemnogene abeparvovec-xioi.[37]

## Benefits and Risks of Risdiplam to Individuals

Daily oral dosing of risdiplam is efficacious in infants and children older than 2 months (see Table 1).[5,38,39] It is the only drug to have been tested in adults up to the age of 60 years.[39] Significant off-target effects have been noted at high doses in preclinical animal studies, including cell cycle inhibition, retinal cystic degeneration, epithelial cell degeneration in the gastrointestinal tract, skin changes, fetal malformations, and degeneration of germ cells in the testes.[40] Systemic administration could theoretically result in better restoration of bulbar and respiratory function than nusinersen and augment SMN in peripheral tissues. Although clinical data suggest that the recommended doses are safe and regulatory agencies have approved the drug with no major warnings (see Table 2), lifelong therapy and longer periods of exposure have the potential for off-target effects. Risdiplam is priced competitively against onasemnogene abeparvovec-xioi and nusinersen (see Table 1). Given its oral administration, risdiplam has the advantage of being more convenient, especially in older patients in whom intrathecal administration may be more challenging because of spinal surgeries and scoliosis, and in these unprecedented times, when hospital and community exposures to viral infections should be minimized for vulnerable neuromuscular patients. Storage and shipping at ambient temperatures are added benefits of risdiplam for worldwide availability and distribution.

## Balancing Benefits and Risks: Assessing Goals of Care

There are no head-to-head clinical trials comparing one treatment to another. There is basic resistance of companies to conduct such studies, as there likely will be winners and losers, although families will benefit by making better choices.

Adults with SMA are in a vulnerable position because of the paucity of FDA-approved drugs for adults with this life-changing degenerative condition. Patients with incurable diseases tend to overestimate benefit and underestimate burden of experimental therapy, which can affect their decision-making capacity.[41] Public perception of medical risk is low,[42] and specifically, publicly perceived risks of gene therapies are increasingly minimized with increasing severity of the disease.[43] Physicians should be aware of this and not shy away from discussing unknowns with patients. They should initiate discussions with patients on their goal; is it to stay up longer in the day, be able to type or read more, have greater endurance and energy for daily activities? Is it to have better verbal communication? Regain motor function? Have fewer falls? One key question is the impact of treatment on QOL, given that intrathecal administration of nusinersen is not without risk. Would other SMN-augmenting therapies be safer and more convenient? Adults with SMA can choose between nusinersen or risdiplam. The more convenient orally administered risdiplam has been studied in clinical trials involving adults, and preliminary 1-year efficacy results in patients up to the age of 60 years suggest stabilization in motor function (see Table 1). If the option of being enrolled in clinical trials on onasemnogene abeparvovec-xioi and/or combination therapy with risdiplam arises, patients need to understand benefits and risks of all therapies and know that clinical trials may exclude patients already on nusinersen. Patients and health care providers must determine whether benefits outweigh the costs for each plan and decide which one is best for them.

Infants and children with SMA are also vulnerable due to the urgency of administering SMN-augmenting treatment as early as possible to reduce irreversible motor neuron degeneration.[44,45] Here the goal is clear: to preserve life and as much future function as possible. Most of the motor neurons are lost by 6 months in SMA type 1,[46] and earlier treatment interventions with nusinersen and onasemnogene abeparvovec-xioi result in better motor and survival outcomes.[47,48] Preconception carrier screening and newborn screening accelerate presymptomatic diagnosis and treatment. For presymptomatic infants with SMA younger than 2 months, what information do physicians and parents need to choose between nusinersen and onasemnogene abeparvovec-xioi? Both drugs have shown efficacy in presymptomatic patients (see Table 1).[49,50] Which therapy is more tolerable at which age? In this era of precision medicine, are physicians, parents, and other stakeholders aware of the durability, risks, and benefits of each of the treatments and possible emergence of extraneuronal phenotypes[51]? Answers to concerns on

**TABLE 3. Summary of Cost Analysis from US ICER and UK NICE**

| | | Best Supportive Care | Nusinersen | | Onasemnogene Abeparvovec-Xioi | Risdiplam |
|---|---|---|---|---|---|---|
| Drug treatment cost over a lifetime | Presymptomatic[a] | — | $10,565,000 | | $2,000,000[b] ($2,125,000)[c] | Not reported |
| | Early onset | — | $2,231,000 | | $2,000,000 ($2,125,000)[c] | Not reported |
| | Later onset | — | $7,634,000 | | N.A. | Not reported |
| Total drug and nontreatment health-related costs over a lifetime | Presymptomatic | $801,000 | $11,929,000 | | $3,264,000[b] ($3,389,000)[c] | Not reported |
| | Early onset | $789,000 | $3,884,000 | | $3,657,000 ($3,782,000)[c] | Not reported |
| | Later onset | $1,442,000 | $9,148,000 | | N.A. | Not reported |
| QALYs | Presymptomatic | 6.25 | 21.94 | | 21.94[b] | Not reported |
| | Early onset | 0.46 | 3.24 | | 12.23 | Not reported |
| | Later onset | 11.34 | 12.28 | | N.A. | Not reported |
| Cost/QALYs gained over best supportive care | Presymptomatic | — | $709,000 | | $157,000 | Not reported |
| | Early onset | — | $1,112,000 | £642,965–£1,397,060 ($860,181–$1,869,035) from NICE | $243,000 | >£50,000 (> $66,891) from NICE |
| | Later onset | — | $8,156,000 | £394,343–£2,112,435 ($527,565–$2,826,089) from NICE | N.A. | > £50,000 (> $66,891) from NICE |
| Annual prices to achieve $150,000 per QALY gained | Presymptomatic | — | $64,800 | | Not reported | Not reported |
| | Early onset | — | $0[d] | | $899,000 | Not reported |
| | Later onset | — | $3,400 | | N.A. | Not reported |

Values are from US ICER unless indicated from NICE. Costs are in US dollars or UK pounds sterling. For UK pounds sterling, US dollar equivalent at November 24, 2021 exchange rate is in parentheses.

Sources: US ICER, https://icer.org/wp-content/uploads/2020/10/ICER_SMA_Final_Evidence_Report_110220.pdf, https://icer.org/wp-content/uploads/2020/10/SMA-RAAG_060519.pdf; NICE, https://www.nice.org.uk/guidance/hst15/evidence/evaluation-consultation-committee-papers-pdf-9191287693, https://www.nice.org.uk/guidance/ta588/evidence/final-appraisal-determination-committee-papers-pdf-6842813869, https://www.nice.org.uk/guidance/gid-ta10612/documents/committee-papers.

[a]Mix of 60% SMA type I, 30% SMA type II, and 10% SMA type III in US ICER analysis.

[b]One-time costs of onasemnogene abeparvovec-xioi with the health care costs and QALYs associated with nusinersen in presymptomatic SMA patients in US ICER analysis.

[c]US ICER used $2 million as an estimate of the drug cost, which was not available when the analysis was done. In parentheses are the estimated costs based on the actual retail price of $2.125 million, as added by the authors.

[d]No threshold prices for nusinersen for thresholds of $300,000/QALY and below, even at zero price for nusinersen in US ICER analysis.

N.A. = not applicable; NICE = National Institute of Health and Care Excellence; QALY = quality-adjusted life-year; US ICER = US Institute for Clinical and Economic Review.

durability and treatment-modified phenotypes will come only with the passage of time. Physicians need to clearly inform parents on the cell targets of each of these innovative therapies and potential clinical implications for their children as they grow up. Risdiplam is currently not approved for infants younger than 2 months, in line with the youngest patient recruited in symptomatic SMA type 1 clinical trials, but may be a future option pending results from ongoing studies in presymptomatic patients. If parents of an infant diagnosed during newborn screening or during the first 2 months of life decide to go ahead with administration of onasemnogene abeparvovec-xioi, they may find limitations on insurance reimbursement for nusinersen and risdiplam.

The financial costs of treatment are substantial (Table 3). In the United States, insurers make their coverage determinations independently. Coverage for the drugs and their procedures differs, based on policy providers. Policy provider restrictions can include age, type of SMA, and location of patient. All 3 drug companies have copay assistance programs for those with commercial insurance and may be able to refer to charitable organizations for third-party assistance. Medicare and Medicaid also provide coverage on a case-by-case basis. In countries with government-paid health care such as those in Europe and Asia, drug companies may work out discounts with governments. For example, the managed access agreements with the National Health Service in the United Kingdom enable a drug to be available for a limited time at a discounted price while waiting for real-world evidence of its effectiveness. However, when drugs are not available or subsidized through government resources, families have to either seek help from companies through expanded access programs, or find a source for private funding to pay for treatment that costs more than their house. These innovative therapies may become financial and emotional burdens for patients and their families. Financial and personal costs will have to be weighed by families when considering the overall impact on QOL.

## Quality of Life

Physicians should ascertain whether parents and patients labor under false hope that SMA therapies will result in a cure. Lifespan and QOL are positively impacted in children with SMA who receive innovative therapies, but long-term implications are unknown and will need to be carefully observed by monitoring systemic function. SMA being a rare disease, it is challenging to quantify changes in QOL, when there is limited long-term effectiveness data in children whose disease would previously be untreatable, and clinical trials are of short duration, with limited randomized or head to-head trials.[52] Assessing health-related QOL in children is inherently challenging, because young children usually do not have the cognitive ability to understand and complete measurement tasks. There are factors that are important in child development, such as the ability to communicate and grasp objects, that will not be detected using generic measures. Other factors important to children, like autonomy, body image, and family relationships, may not be captured in routine measurements like the Pediatric Quality of Life instrument. Parents as proxies may not represent patients adequately and instead capture their own anxieties due to the illness.

In adults, the impact of nusinersen on QOL is less clear. Health-related QOL measures are heavily weighted toward physical function. Maintaining stability of function is rated as extremely important,[53,54] although global QOL is determined not just by physical but also by psychological, existential, and support factors.[55] Physicians should be aware that patient QOL may be rated higher by the patient than by others.[56] Although motor improvement is minimal in adults with SMA, stabilization of motor function and improvement of energy and endurance can help patients to continue to work, interact with loved ones, and meet their existential and interpersonal goals. These experiences can bring more meaning to their lives. Examples of these clinically meaningful benefits of treatment that are not captured by disease assessment scales include increased energy levels allowing patients to stay up longer in the day and perform better at work or school, maintaining voice strength and the ability to talk, typing for longer periods of time on the computer without getting fatigued, or being able to walk longer on crutches rather than using a wheelchair.[14] The range of impacts of diminished educational opportunities or reduced integration into society on patients' QOL is also difficult to capture using available measures.

Importantly, SMA affects the health-related QOL not just of patients but also of their families, carers, and wider communities.[57] Patients may be entirely dependent on their care providers. For example, parents and the extended family who care for the patient may experience sleep deprivation associated with the need to turn their infants during the night. They may expend tremendous emotional and physical effort providing the intensive care and support required to maintain mobility and function of SMA patients for as long as possible. Care providers may end up having to work part-time or giving up work. This is challenging to quantify, as the methodology for assessing caregivers' QOL and economic burden is not well developed. Parents may feel guilty if long-term drug side effects occur in their children that impact peripheral tissues, such as cardiovascular or bone health, financial

means limit access to life-changing therapies, or incomplete rescue of motor neurons results in significant physical impairments for a lifetime, which could be regarded as prolongation of suffering. They may feel guilty if benefit from one treatment was suboptimal or not durable and insurance subsequently declined to pay for another.

## Justice: Broader Societal Perspective

Biogen and Novartis have received criticism for setting high drug prices for nusinersen and onasemnogene abeparvovec-xioi, respectively. Roche has so far avoided much criticism by pricing risdiplam competitively against the other two drugs, but the competitive cost of risdiplam is high by definition. Using the principle of justice, the needs of the individual must be weighed against the needs of the collective, to consider in the wider economic picture whether it is fair for society to fund highly expensive life-sustaining treatment for a small group of patients. The approach to cost-effectiveness of the US Institute for Clinical and Economic Review (US ICER) and UK National Institute for Health and Care Excellence (NICE) is to calculate the incremental cost of treatment relative to the incremental benefit over best supportive care for these innovative drugs, known as the incremental cost-effectiveness ratios (ICERs).[58] A very high-cost treatment that does not have a significant effect on health-related QOL would have a large ICER, which would be financially unsustainable to fund. Quality-adjusted life-years (QALYs) are used to quantify health-related QOL. In the United Kingdom, the maximum acceptable ICER is £20,000–£30,000 (US $26,757–$40,135) per QALY (NICE guidelines[59]), and in the United States, the maximum acceptable ICER is US $100,000–$150,000 per QALY (US ICER recommendations[60]). Using these recommendations, nusinersen and onasemnogene abeparvovec-xioi exceed the cost-effective threshold for US ICER and all 3 drugs exceed the threshold for NICE (see Table 3),[8,61–64] with minimum ICERs of US $709,000 and £394,343 (US $527,565) for nusinersen, US $157,000 and £177,061 (US $236,878) for onasemnogene abeparvovec-xioi, and more than £50,000 (US $66,891) for risdiplam; thus, all 3 drugs are overpriced. Presymptomatic treatment is more cost-effective than symptomatic early and late onset SMA treatment, because QALYs are substantially increased. Of note, durability of onasemnogene abeparvovec-xioi treatment has yet to be confirmed beyond approximately 5 years,[30] and costs will rise substantially in the event that additional adjunct SMN-augmenting therapy is required. Because most of the total treatment costs relate to the expense of the innovative drug, discounting the price of the drugs would significantly reduce the ICERs to levels accepted as cost-effective.

Pharmaceutical companies need to be able to recoup their huge costs of research and development and turn a profit on orphan drugs.[65] If pharmaceutical companies do not realize a profit, they may decide to change strategies and stop investments in drug development for rare diseases. Valuation of a new ground-breaking treatment depends not just on its opportunity cost, but also on patient benefit over a lifetime. QALYs are unlikely to capture all the important aspects of health-related QOL in SMA patients and their care providers because of the difficulties with measuring all clinically meaningful treatment benefits, and challenges with measuring care provider QOL. Given the rarity of SMA, there are limited data quantifying the true cost to the health and social care systems, and lost productivity of patients, care providers, and the wider society. Parents of children with SMA would argue that the drugs are cost-effective when compared to the cost of a child's life and future, and financial costs of a lifetime of home physical, occupational, and speech therapy, full-time care-givers, ventilation, adaptive equipment, and recurrent hospitalizations, quite often in intensive care units. Cost-effectiveness also depends on patient access programs and other commercial agreements, the nature and extent of the resources needed to enable the new medications to be used, and whether there are significant benefits other than health, such as social and economic benefits.

Transparency should be sought on how to price orphan drugs, and the long-term implications of orphan drug pricing strategy on society should be considered. Rising costs of health care will be passed on to the taxpayers or to privately insured individuals as higher premiums. Ultimately, rationing in the form of rising deductibles and copayments will occur, and contribute to the economic challenges that patients already face. These are broad societal issues that physicians have a duty to consider, as they lie within the scope of the ethical principle of justice.

## Conclusions

The therapeutic landscape for SMA now includes 3 FDA- and EMA-approved therapies in the past 5 years. Early treatment of presymptomatic infants yields the best clinical outcomes. Treatment of symptomatic patients with SMA is complicated by the clinical heterogeneity of the condition in children and adults, unknown real-world safety and durability outcomes when receiving lifelong therapies, and limited clinical efficacy data in adults. There is a need for head-to-head and combination therapy

clinical trials in presymptomatic and symptomatic patients to enable patients, caregivers, and physicians to make informed drug comparisons and determine risks versus benefits, but there are practical limitations in getting pharmaceutical companies to do head-to-head comparisons, because there will be winners and losers. Physician-led clinical studies may help to fill in these gaps. None of these innovative therapies is curative. There is a need for long-term systemic observational studies of treated patients to understand treatment-modified phenotypes and the long-term disabilities potentially caused by partially rescuing motor neuron degeneration in severely affected symptomatic patients.

Although SMA is typically regarded as a pediatric disease, adult neurologists should be prepared to see and manage treated SMA type 1 patients who are likely to survive into adulthood and be aware of possible treatment-modified phenotypes based on SMA pathology and the cell targets and mechanisms of actions of each of the innovative SMN-augmenting therapies. A multidisciplinary team approach may be required to monitor for potential extraneuronal phenotypes and manage possible peripheral organ dysfunction in treated SMA patients. Physicians are patient advocates and have a duty to respect autonomy and be guided by the principles of beneficence, nonmaleficence, and justice. They need to take time to understand the basic science behind the clinical trials that leads to drug approval and compassionately frame medical facts in the context of patients' needs and goals, as a path toward shared decision-making. They can advocate on behalf of their patients to stakeholders such as third-party private insurers, government or state-run public insurance plans, and pharmaceutical companies for adjunct therapy, provision of life changing treatment to all who may benefit, and keeping orphan drug prices affordable and financially sustainable to society. We need to convey the knowledge and gaps in knowledge to patients in clear layperson language so that they may make an informed decision. Although there are more questions than answers, as physicians, we need to ensure that discussions with parents and adults with SMA concerning therapies follow the ethical principles described here to facilitate the best QOL and benefit versus risk ratio for the patient.

## Author Contributions

C.J.J.Y. and B.T.D. contributed to the conception and design of the article. All authors contributed to the interpretation of studies included in the article. All authors contributed to drafting the text and preparing the tables and figure.

## Potential Conflicts of Interest

C.J.J.Y. has nothing to report. Z.S. has received research support from and served as a scientific board member for Biogen (manufacturer of nusinersen). D.C.D.V. has served as advisor/consultant for AveXis (developer of onasemnogene abeparvovec-xioi), Biogen (manufacturer of nusinersen), and Roche (manufacturer of risdiplam); and received clinical trial funding from Biogen (manufacturer of nusinersen). B.T.D. has served as an ad hoc scientific board member for Biogen, AveXis, and Roche/Genentech (manufacturers of nusinersen, onasemnogene abeparvovec-xioi, and risdiplam, respectively); and is FIREFISH study Steering Committee Chair for Roche (manufacturer of risdiplam).

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