a Practical Guide to Ethical Decision-Making Regarding Drug Coverage for Rare Diseases: Case Study of Nusinersen Therapy for Spinal Muscular Atrophy

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A Practical Guide to Ethical Decision-making Regarding Drug Coverage for Rare Diseases: Case Study of Nusinersen Therapy for Spinal Muscular Atrophy

by

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Harvard Medical School Class of 2019

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Area of Concentration: Medical Ethics

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I have reviewed this thesis. It represents work done by the author under my supervision and guidance.

Faculty Supervisor’s Signature
ABSTRACT

Nusinersen for the treatment of Spinal Muscular Atrophy was among the first definitive treatments for neurodegenerative conditions to come to market as of 2016. The drug’s rapid U.S. governmental approval came on the heels of the improvement in motor milestones observed in its two leading clinical trials, infusing newfound hope into a disease community that has long endured slow, often painful motor decline and early death. Genetic therapies have welcomed a tremendous amount of promise into the medical sphere – offering patients reductions in their disease burdens, and in some cases, the hope of cure. But the more individual and targeted the drugs become, the more important it is to consider their benefits carefully in a monetarily constrained atmosphere. In the case of Nusinersen, for example, the United Kingdom’s National Institute for Health and Care Excellence (NICE) has ruled as of October 2018 in favor of denying administration of the drug for patients in the United Kingdom, given the weighing of the drug’s existing clinical trial data against the need to preserve cost-effectiveness and fair allocation of resources of the National Health Services budget. With the Centers for Medicare and Medicaid Innovation already in the early stages of piloting global bundling pay structures, the possibility of similar constraints to the drug’s ongoing administration in the United States are coming to the fore, particularly for those patients that are unable to or prohibited from paying out-of-pocket or balancing paying by pharmaceutical firms. This is why, now, more than ever, the ethical frameworks surrounding coverage decisions must be critically investigated. This paper, therefore, will use Nusinersen therapy as a case study through which to examine and raise questions about the ethics utilized in decision-making contexts regarding drug coverage determinations for rare diseases. It will first provide a clinical overview of the drug’s function, relevant clinical trial data, and general ethical considerations in administration, and will then transition into a broader discussion on the ethics leveraged in drug coverage determinations using two ethical axes—those of cost-effectiveness analysis and medical futility. The hope, in doing so, will be to prepare ethicists, physicians, caretakers, and patients alike for what is bound to become part of the national policymaking agenda moving forward.

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GLOSSARY OF TERMS

ACA Patient Protection and Affordable Care Act (2010)
ACT UP AIDS Coalition to Unleash Power
ASO Antisense Oligonucleotide
CEA Cost-Effectiveness Analysis
CFTR Cystic fibrosis transmembrane conductance regulator
CHOICE CHOosing Interventions that are Cost-Effective
CMMI Centers for Medicare and Medicaid Innovation
CUA Cost-Utility Analysis
DMD Duchenne Muscular Dystrophy
EGFR Epidermal Growth Factor Receptor
FDA U.S. Food and Drug Administration
HAART Highly Active Antiretroviral Therapy
HFSME Hammersmith Functional Motor Scale-Expanded
HINE Hammersmith Infant Neurologic Exam
HIV/AIDS Human Immunodeficiency Virus/ Acquired Immunodeficiency Syndrome
ICER Incremental Cost Effectiveness Ratio
NICE National Institute for Health and Care Excellence
PCORI Patient Centered Outcomes Research Institute
QALY Quality Adjusted Life Year
DALY Disability Adjusted Life Year
RNA Ribonucleic Acid
SMA Spinal Muscular Atrophy
SMN1 Survival Motor Neuron-1 gene
SMN2 Survival Motor Neuron-2 gene
WHO World Health Organization
INTRODUCTION

In 2016, Ionis Pharmaceutical and Biogen’s Nusinersen (Spinraza) for the treatment of Spinal Muscular Atrophy was among the first antisense oligonucleotide (ASO) drugs for neurodegenerative conditions to come to market. The drug’s rapid U.S. governmental approval came on the heels of the improvement in motor milestones observed in its two leading clinical trials, infusing newfound hope into a disease community that has long endured slow, often painful motor decline and early death.

Drugs leveraging the ASO chemistry—targeted biologics aiming to restore normal gene products through forming complementary sequences with problematic components of a given gene’s messenger RNA—have been on the scene for over two decades. In fact, as early as 1998, the Food and Drug Administration (FDA) authorized Isis Pharmaceuticals and Novartis Ophthalmics’ Fomiversen, which was utilized as a therapy to treat cytomegalovirus retinitis – a disease that was globally rampant prior to the widespread implementation of HAART for HIV/AIDS patients. Since this time, ASO drugs have entered trials across multiple different medical domains. The industry itself is now burgeoning and is projected to grow exponentially in the coming years.

Genetic therapies have introduced a tremendous amount of promise into the medical sphere – offering patients reductions in their disease burdens, and in some cases, the hope of cure, usually understood as a complete reversal or arrest in some progressive disease processes. But the more individual and targeted the drugs become, the more important it is to consider their benefits carefully in a monetarily constrained atmosphere. In the case of Nusinersen, for example, the United Kingdom’s National Institute for Health and Care Excellence (NICE) has ruled as of October 2018 in favor of denying administration of the drug for patients in the United Kingdom,

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given the weighing of the drug’s existing clinical trial data against the need to preserve cost-effectiveness and fair allocation of resources of the National Health Services budget. With the Centers for Medicare and Medicaid Innovation (CMMI) already in the early stages of piloting global bundling pay structures, the possibility of similar constraints to the drug’s ongoing administration in the United States are coming to the fore, particularly for those patients that are unable to or prohibited from paying out-of-pocket or balancing paying by pharmaceutical firms. This is why, now, more than ever, the ethical frameworks surrounding coverage decisions must be critically investigated. This paper, therefore, will use Nusinersen therapy as a case study through which to examine and raise questions about the ethics utilized in decision-making contexts regarding drug coverage determinations for rare diseases, which are defined as conditions affecting 200,000 or fewer people globally. It will first provide a clinical overview of spinal muscular atrophy along with the details of the drug’s intended genetic target, relevant clinical trial data, and general ethical considerations in administration, and will then transition into a broader discussion on the ethics leveraged in drug coverage determinations using two ethical axes—those of cost-effectiveness analysis and medical futility. The hope, in doing so, will be to prepare ethicists, physicians, caretakers, and patients alike for what is bound to become part of the national policymaking agenda moving forward.

**SPINAL MUSCULAR ATROPHY AND NUSINERSEN: THE BASICS**

Spinal Muscular Atrophy (SMA) is a rare, neurodegenerative condition affecting 1 in 6,000 to 10,000 individuals worldwide. The disease is caused by the loss of motor neurons in the anterior horn of the spinal cord, which leads to muscle atrophy, wasting, and ultimately, impaired respiration and premature demise. The majority of cases are due to mutations in the Survival Motor Neuron-1 (SMN1) gene, which is responsible, along with the related gene SMN2, for producing Survival Motor Neuron protein that plays the most significant role in maintaining

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physiologic motor neuron function. SMA types are defined by the age at onset of symptoms, with earlier diagnosis typically corresponding to increased disease severity. Type 1 patients show motor deficits at birth or within the first few months of life, Type 2 between the ages of six to eighteen months, Type 3 in childhood or adolescence, and Type 4 at age thirty or above. Type 1 patients typically experience “hypotonia…diminished limb movements…tremors…swallowing and feeding difficulties…impaired breathing…and the vast majority usually die of respiratory failure before the age of two.” A 1997 study of 569 German and Polish SMA patients indicated that 68% of Type 2 patients were alive at 25 years of age and that Types 3 and 4 patients appeared to have a normal life expectancy.

Since the identification of the genetic underpinnings of SMA in 1995 by Lefebvre et al, there have been a number of different genetic approaches to treatment that have entered clinical trials. It was not until over twenty years later, however, in December 2016, that the first definitive genetic therapy — Nusinersen (Spinraza) — was approved by the FDA and by other global drug approval agencies for widespread treatment of the SMA population-at-large. Prior to this, patients were typically treated with more conservative management of symptoms, including through being provided nutritional supplementation, pulmonary support, and orthopedic stabilization, if required.

As a drug designed as a rare disease therapeutic, Nusinersen received fast-tracking through the FDA approval process under the mandate of The Orphan Drug Act. Ratified in 1983, this legislation affords pharmaceutical companies working in the rare disease sphere drug-specific priority reviews and exemptions from certain fees by the FDA, the ability to present data identifying surrogate endpoints in the context of clinical trials, tax credits for various research-
related expenditures, and seven years of market exclusivity should a given drug receive FDA approval. It was borne out of an era in which the cost of drug research more broadly skyrocketed following the passing of the Kefauver-Harris Amendment in 1962, which tightened regulations surrounding safety and efficacy data required for drug approval. The Amendment represented a federal response to the U.K. scandal associated with the drug Thalidomide’s highly publicized role in contributing to defects in fetal organogenesis. In light of the fact that pharmaceutical companies were forced to comply with significantly more stringent guidelines in order to get drugs to market, the 1962 ruling had both positive and negative implications. On the one hand, the safety and efficacy of drugs receiving FDA approval were much more assured, leading to better outcomes and fewer adverse events for patients. On the other, the newly required expenses on the part of pharmaceutical companies that had to be put toward the ensuring of satisfactory data for drug approval translated into the progressive casting aside of drug research for rare diseases, which was perceived to be much costlier upfront. This consequently prompted a group of patients with rare diseases and their families to band together to form the National Organization for Rare Disorders (NORD) in 1982, which, in an attempt to stimulate growth in the area of drug research for rare diseases, advocated for what ultimately became the passing of the 1983 orphan drug legislation. This law re-instilled in pharmaceutical companies the hope of good returns for rare disease investments while at the same time granting them a significant amount of bargaining power regarding downstream drug pricing. At the time of its approval, for example, Nusinersen’s price tag for U.S.-based consumers was set at $125K per administration, amounting to $750K in year one and $375K annually afterward. This is as compared to the $23,331 versus $111,820 average annual costs of non-orphan and orphan drugs, respectively.

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Nusinersen is an antisense oligonucleotide drug targeting the SMN2 gene, which accounts for only about 10% of the production of Survival Motor Neuron protein at baseline. In unaffected individuals, SMN1 produces the majority of functional SMN protein, while SMN2 serves as the “back up” gene. The discrepancies between the two genes in their respective abilities to produce functional SMN proteins rests in a single nucleotide polymorphism in SMN2 (840.C\rightarrow T) that causes alternative splicing, consequent elimination of exon 7, and resultant production of largely non-functional SMN protein products. In SMA, mutations in the SMN1 gene dramatically reduce circulating levels of functional SMN protein, shifting the onus of SMN protein production to SMN2. Nusinersen, therefore, works to target the splicing defect of SMN2, allowing for more effective inclusion of exon 7, and consequently upregulating functional SMN protein production (See Figure 1). The drug requires intrathecal administration through lumbar puncture, with 4 initial loading doses delivered at 14-day intervals, and maintenance doses necessary every 4 months thereafter.\footnote{Spinal Muscular Atrophy Support UK [Internet]. SMA SUPPORT UK AT THE CURE SMA CONFERENCE 2015; c2015 [cited 2018 Sept 21]. Available from http://www.smasupportuk.org.uk/blog/treatments-research/sma-support-uk-at-the-cure-sma-conference-2015} 

\begin{figure}[h]
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\caption{An overview of Nusinersen function on SMN protein production.\footnote{Ibid.}}
\end{figure}

Nusinersen’s efficacy was shown through demonstration of improvement and/or maintenance of motor milestones in two independent phase III studies—ENDEAR for infantile-onset SMA
(defined as onset of symptoms ≤6 months of age) and CHERISH for later-onset SMA (individuals ages 2-12, able to sit independently but never able to ambulate independently). Both studies were multicenter, randomized, double-blind, and sham-procedure controlled. ENDEAR analyzed the proportion of responders (patients showing an improvement in motor milestones according to the Hammersmith Infant Neurologic Exam (HINE) in 121 Type 1 SMA patients over a 13-month period. Similarly, CHERISH examined 126 patients’ least-squares mean changes from baseline in the Hammersmith Functional Motor Scale-Expanded score (HFSME) following 15 months of treatment. Ultimately, ENDEAR showed that 51% of the population receiving Nusinersen clinically responded to treatment versus 0% in the sham arm. It also showed a statistically significant 47% reduction in risk of death or requirement of permanent ventilation at the time of the trial completion. Similarly, in the CHERISH trial, 57% of patients administered Nusinersen (versus 26% in the control group) demonstrated an increase by at least 3 points on the HFSME at the end of the trial. These positive findings, in conjunction with significant advocacy by SMA patient groups, prompted the FDA’s priority review and subsequent fast-tracked approval for dissemination and administration of the drug at the end of 2016.

The legal go-ahead for drug administration, however, was fraught with ethical uncertainty. In their February 2018 article on the Ethical Challenges Confronted When Providing Nusinersen Treatment for Spinal Muscular Atrophy, Burgart et al. outline six points of ethical consideration regarding the drug’s administration, including those of the drug’s cost, evidence-base, and associated informed consent, along with a consideration of treatment allocation, fair distribution of responsibilities, and transparency with stakeholders. With regard to cost, they discuss the difficulties presented by the sheer expense of the drug. It is within this realm that they express unease regarding the determination of an individual patients’ receipt of the drug by the financing

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payer, consequently “generating concerns for the distribution of health care.” In addition, they comment on the role of the drug’s high price in influencing families to forgo treatment altogether or in its contribution to “financial strain.” From an evidence-based perspective, the authors note the lack of generalizability of study data given small sample sizes of the ENDEAR and CHERISH trials (n=121 and n=126, respectively). They also discuss the application of the drug to a population with “limited residual strength” that was not explicitly tested in the clinical trials, raising “new questions…regarding benchmarks for effective treatment.” And due to the limited data available on the drug’s efficacy, they further delve into the murkiness of whether or not consent is truly informed.

Though we are in a moment when patients in the United States are able to attain the drug irrespective of motor status, the cost of administration has become an increasing concern. Given the United Kingdom’s definitive refusal as of October 2018 to provide administration of Nusinersen to their SMA population citing a lack of cost effectiveness, and coupled with the probable adoption of a global bundling insurer model for Medicaid, the ethics of drug provision is imperative to consider. From a cost perspective, what will be the criteria by which health insurers decide on coverage? And with respect to individual patients, what role will the high cost of the drug play in pushing patients and their families toward forgoing therapy when insurance does not approve of it? From an efficacy standpoint, what are the benchmarks that should be utilized to define treatment response? Should these benchmarks be imposed by a governing body or by the patient him/herself? Should provision of the drug in patients who show any response be based on patient choice in order to preserve patient autonomy? And with regard to informed consent, when do risks outweigh benefits? How do we define when stopping treatment is preferable to continuing? Whose role is this? These are but a few questions that are necessary to address in an ongoing discussion about how Nusinersen ought to be distributed, if at all.

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22 Burgart et al, 189.
23 Ibid.
24 Ibid.
In order to facilitate decision-making regarding coverage to allow for the continued availability of Nusinersen for patients, it is important to reflect on the full range of ethical perspectives that may contribute to such decision-making efforts. Namely, the frameworks for use in such contexts must take into consideration both consequentialist and non-consequentialist viewpoints, particularly given their varying contributions to arriving at definitive conclusions in drug coverage rulings. As noted in the paper’s introduction, the two axes that will be explored here will be centered on helping incorporate two distinct areas of concern regarding the drug’s continued administration in SMA patients. First, the ethics surrounding the use of cost-effectiveness analysis will be delved into, which is of utmost relevance given its role in the decision-making surrounding drug coverage in the U.K. and its potential U.S.-based implications. Following this, the notion of medical futility will be explored as a counterpart, helping introduce another conceptual framework through which to think about the validity of the drug’s ongoing administration. For some decision-makers, the framing of a decision largely through cost-effectiveness analysis may present as heartless; in parallel with this, however, the use of medical futility as a driving metric may be equally difficult in this context, if not seemingly morally less distressing on the surface.

**THE COST-EFFECTIVENESS ANALYSIS FRAMEWORK**

The incorporation of cost-effectiveness into medical decision-making came to center stage in the 1990s, largely catalyzed by the launching of the World Health Organization’s 1998 CHOICE project that was aimed at “providing policy makers with evidence for deciding on interventions and programs which maximize health for the available resources.” The initiative lay the foundation for what ultimately became a formalized country-level guide to cost-effectiveness analysis by 2003, catapulting many governments world-wide into considering much more seriously the issue of cost as related to both medical care and pharmacologic agents.

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In the medical realm, cost-effectiveness analysis (CEA) has come to represent a form of economic inquiry in which two distinct medical interventions that ideally lead to the same health outcome are compared through evaluation of both cost and effectiveness. This method of analysis is particularly pertinent with regard to evaluation of the ratio of change in cost to change in effectiveness of new pharmaceuticals relative to those already well-established on the market (this ratio is often referred to as the incremental cost effectiveness ratio or ICER). Relatedly, cost-utility analysis (CUA) represents a subset of CEA that is often examined in tandem with ICER calculations and that assesses cost relative to utility as a primary outcome measure. Here, utilities signify “preferences individuals or society may have for any particular set of health outcomes…expressed as numerical values between 0 and 1.” In developed countries, the utility typically examined in CUA is that of the quality adjusted life year (QALY), which takes into consideration the additional length of lifetime that a given pharmaceutical treatment provides a patient balanced against the quality of the time as valued through a 0-1 scale determined by preference-based weights (0 representing death and 1, perfect health). The CUA metric largely utilized in developing countries is that of the disability-adjusted life year (DALY), which represents a sum of years of life lost due to premature death and years of life lost to disability. In the disability component of the calculation, it similarly incorporates a 0-1 scale to quantify quality of life (0 representing full health and 1, death), with weighting determined by a set of standardized disability weights versus the preference-based weights leveraged in the context of QALY calculations. Thus, depending on the utility metric examined, the goal of CUA is to assess either the cost per QALY gained or the cost per DALY avoided for a given patient. According to WHO-designated cost-effectiveness thresholds, an intervention that costs equal to or less than three times the national GDP per capita per DALY avoided or QALY gained is considered to be cost-effective. In the United States, therefore, WHO deems roughly $150,000 or less per QALY gained to be reflective of cost-effectiveness.

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30 Ibid.

With the cost of Nusinersen becoming an escalating worry from a budgetary allocation standpoint, the United Kingdom’s Department of Health and Social Care requested that the National Institute for Health and Care Excellence (NICE) evaluate the cost effectiveness of the pharmaceutical in hopes of providing guidance on forthcoming coverage. In August, 2018, NICE published a preliminary report stating that it did not recommend Nusinersen for coverage, citing “no long-term evidence...[and] uncertain...long-term benefits.” This was based on a lack of clarity about improvement in long-term survival rates, resulting in CUA estimates between a minimum of 400,000-600,000 pounds per QALY gained that had the possibility of being higher based on the limited available trial data for analysis. In conjunction with this, the document spoke to the organization’s inability to calculate the ICER given that “the patient access scheme for Nusinersen was commercial in confidence.” Thus, NICE concluded that “the very high cost of Nusinersen...[would translate into] significant financial risk to the National Health Service if the committee were to recommend a technology for routine use that may not be cost effective,” consequently justifying their denial of the drug from an insurer standpoint. The NICE decision, which was finalized in October, 2018, sparked a significant amount of disquiet within the SMA community, both in the U.K. and globally, as it represented the first legislative ruling attributed to SMA therapy that defended a largely utilitarian approach.

In the United States, both private and public sectors have largely eschewed formalized integration of cost-effectiveness analysis into drug reimbursement decisions. This is not to say that there have not been any historical attempts at incorporation of such into decision-making strategies for drug coverage, including through the establishment of the 1978 National Center for Health Care Technology, which was geared toward assessment of the “safety, effectiveness, and cost effectiveness of...health care technologies.” The Center, however, was unable to remain functional for an extended period given the staunch opposition that it received through public lobbying by the American Medical Association and the Health Industry Manufacturer’s...
Association, the largest national representative of medical device companies, both of whom felt that it represented “an unnecessary bureaucratic appendage.”

On a related and contemporary note, the passing of the 2010 Patient Protection and Affordable Care Act saw the founding of a similar initiative in the form of the Patient Centered Outcomes Research Institute (PCORI) aimed at “assist[ing] patients, clinicians, purchasers, and policy-makers in making informed health decisions by advancing the quality and relevance of [medical] evidence.” Yet, law makers opposed to the utilization of cost-effectiveness analysis to inform federal decision-making rallied for legislation that mandated that the PCORI be unable to use “certain cost-effectiveness methodologies…[or to] frame its research findings as mandates, guidelines, or recommendations for payments, coverage, or treatments.” This has largely hindered progress in the realm of advancing the role of CEA in federally-funded drug coverage rulings. This lack of consideration of cost-effectiveness, however, is juxtaposed with the ACA’s parallel development of the Center for Medicare and Medicaid Innovation (CMMI), which is aimed explicitly at developing “payment and service delivery models that have the protentional to reduce…cost…while preserving or enhancing quality of care for beneficiaries.” In this context and with regard to Nusinersen, for example, the threat of a Medicaid-based global bundling payment scheme rollout in which hospitals or vertically-integrated Accountable Care Organizations will receive episodic payments to manage large groups of individuals’ patient care will necessitate utilization of cost-effectiveness analysis to make drug coverage and other treatment decisions. Thus, we are in an era in which we cannot continue to maintain a philosophy of avoidance, in which we continue to “avert our eyes…and kick the can of cost-consciousness farther down the road.”

There are a number of key arguments through which those not in favor of the utilization of CEA lay their claims. First and foremost, these stakeholders feel that placing a significant emphasis on

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36 Ibid.
cost-effectiveness translates into both a loss of autonomy for patients and a hindrance to pharmaceutical innovation, in that patients are prevented from freely selecting between different therapy options for a given disease process and pharmaceutical companies are less incentivized to pursue certain projects based on the understanding that their profits for a given drug could potentially be severely curbed by legislation.\(^3\) Relatedly, they maintain a broad-based belief that CEA overall insufficiently considers “social concerns such as prioritizing the sick, reducing inequalities in health, or addressing the well-being of future generations.”\(^4\) In this vein, proponents of a largely non-CEA guided approach also place substantial weight on the ‘rule of rescue,’ a moral imperative first outlined by A.R. Jonsen in 1986 that describes the necessity to provide aid to those who need it most irrespective of the cost and in lieu of consideration of what could potentially be a much greater health benefit to society.\(^5\) One of the most pertinent exemplars of such, which also highlights what Norman Daniels has coined the ‘Aggregation Problem,’ played out in the 1990s through the Oregon Medicaid Program’s implementation of cost-effectiveness analysis to make determinations about coverage of various procedures for its enrollees. Through the use of CEA, they developed a scheme in which tooth capping would take coverage precedence over appendectomy given that it was much more likely to maximize societal health benefits.\(^6\) In other words, the utilitarian perspective utilized in this context sought to “minimize[e] the aggregate burden of disease and maximiz[e] the aggregate health of the population without regard to the resulting distribution of disease and health, or who gets what benefits.”\(^7\) Thus, in an effort to provide patients with access to basic healthcare needs, the state inadvertently created a dilemma that exposed the negative implications of rationing.\(^8\)

Consequently, the Oregon example continues to be cited into the present day to demonstrate the

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pitfalls of the use of CEA in a healthcare context. This exemplar as caveat coupled with the above arguments has resulted in a very cautious use of CEA in an American context.

Perhaps one of the other reasons for which the use of cost-effectiveness in making coverage determinations has not gained traction in the U.S. rests in the multi-faceted aspects of the FDA drug approval process itself; assessment of effectiveness of pharmaceuticals is certainly a large component of such, but patient activism has also become increasingly contributory and influential to approval decisions. This precedent was set as of the late 1980s, when the patient advocacy collective known as the AIDS Coalition to Unleash Power (ACT UP) held a highly successful demonstration in which they shut down the Food and Drug Administration Headquarters and demanded a faster, more streamlined approach to approval of HIV/AIDS treatment modalities. Their actions catalyzed a much more formalized and assertive role for patient advocacy within the realm of drug approvals moving forward. Yet, it also paved the way for FDA decision-making that many have argued has become far too swayed by emotivism.

Take, for example, the accelerated approval of Eteplirsen (Exondys 51) by the FDA in 2016 despite significant pushback from scientists and physicians alike who worried that the evidence of the drug’s efficacy was lacking. In fact, Sarepta pharmaceuticals only submitted a sole n=12 study to the FDA (with n=4 being controls receiving a placebo) and did not examine as primary end point improvement in motor function but rather elevation in protein thought to be attributed to the disease process. Interestingly, the provision of such a surrogate endpoint is acceptable proof of efficacy under the accelerated approval track for FDA drugs designed for diseases that are “serious and life-threatening illnesses [and] that lack satisfactory treatment.” In this context, the FDA stipulates that the “laboratory findings or signs…[do not have to be] a direct measurement of how a patient feels, functions, or survives, but [can be those that] are considered likely to predict benefit.” Yet, even within this frame, the study data presented was minimal,
and the ultimate receipt of FDA drug approval of Eteplirsen was largely due to the lobbying efforts of a highly determined group of Duchenne Muscular Dystrophy patient advocates. Children involved in the initial clinical trial were wheeled up to the stage at the FDA drug-approval hearings, creating a convincing visual plea for the granting of drug approval (See Figure 2). This case has therefore become “a sterling example of the emerging tug of war between patient advocates and drug regulators.”

Figure 2. DMD patients speak at a public FDA hearing on Eteplirsen in 2016.

Advocacy on the part of Spinal Muscular Atrophy patients and families similarly contributed to the passing through the FDA approval process of Nusinersen just months after Eteplirsen met approval on a national stage. In this scenario, again, the approval came in lieu of the weakness of the evidence of the drug’s efficacy provided by Ionis and Biogen in the drug’s approval application, which was limited due to the small sample sizes used (n=121 in ENDEAR and

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n=126 in CHERISH), the lack of inclusion of patients with later onset SMA (Types 3 and 4) for whom the FDA approved the drug despite no designated clinical trial data, and the short lengths of follow up time of patients enrolled in the trials (13 months and 15 months, respectively). What this has created, therefore, is a situation in which there is a lack of robustness of the effectiveness quotient of the drug from which ICER and CUA calculations are derived. Coupled with the large price tag of the drug, cost-effectiveness analysis is surely to conclude that the drug is not cost-effective.

In line with this, it is important to discuss the exorbitant baseline cost of Nusinersen as well as of other biologics designed for rare diseases. This is also contributory to the lack of cost-effectiveness but is a much more difficult variable in the calculations to address head-on. Many pharmaceutical companies argue that the prices of such drugs reflect the high costs of their development and the reduced possibility of downstream returns given the small patient samples for which the drugs are directed. Yet, the Department of Health and Human Services refuted these claims in a December 2016 report to Congress, stating that “in reality, the prices charged for drugs are unrelated to their development costs…[and are solely geared toward] maximiz[ation of] profit.” In conjunction with this, they identified that orphan drug development costs were estimated at $1 billion versus $2.6 billion for mainstream drugs and that drug sales for these therapeutics are slated to comprise roughly 20 percent of total drug sales for pharmaceuticals by 2020, with a projected $178 billion dollars in revenue by this time. The report consequently highlighted the fact that with regard to the Orphan Drug Act’s generous benefits to pharmaceuticals undertaking rare disease projects, “the price spiral—and the loopholes in the approval process—have undermined the spirit of a well-intentioned law.”

Juxtaposed with this is the recognition of a tenuous balance between the desire to curb costs on a national scale while also continuing to ensure research and drug development in a space that was previously severely impacted by legislation (i.e. 1962 Kefauver-Harris Act). Thus, while there may be ways that we can strategize as to how to negotiate prices down with pharmaceuticals, we

also do not want to create an atmosphere in which we reflexively deter the development of future rare disease projects.

Despite the difficulties posed by pharmaceutical-instituted drug pricing, we must acknowledge that we are now in an era in which there is an inevitability to addressing the cost of medical interventions, particularly as the total U.S. spending in the healthcare realm continues to grow, with a 3.9 percent increase in 2017 bringing the total cost to 3.5 trillion dollars or 17.9 percent of gross domestic product.\(^5\) Relatedly, we cannot continue to skirt the issue of whether or not to incorporate cost-effectiveness analysis into the procedural backbone of determinations of drug coverage, even if there may be challenges inherent in doing so from the standpoint of squelching pharmaceutical innovation and in light of the fact that most U.S.-based ethicists and decision-makers in these scenarios believe much more strongly in the notion of deontological or duty-based ethics as first brought forth by Immanuel Kant and explored more contemporarily by Frances Kamm.

Given the newfound cruciality to cost considerations, it is most ethically sound, therefore, to embrace a fairness-based approach to coverage-associated decision-making, in which there is, at the very least, a clear “procedure for what counts as a fair action.”\(^5\) In his 2000 article published in the British Medical Journal, Norman Daniels expands on this by way of introducing the notion of ‘accountability for reasonableness,’ which acknowledges the push and pull between different sides in decision-making in pluralist societies. As such, he speaks to the fact that “in the absence of consensus on principles, a fair process allows us to agree on what is legitimate and fair.”\(^5\) Components of ensuring such a process center on “transparency…[ability to make] appeals…[and provision of] procedures for revision.”\(^5\) In adopting this approach, we can better promote the use of CEA; if there is assuredness among those influential to policy-making that the procedures of drug coverage decision-making are morally permissible, assessment of cost as


\(^{5}\) Ibid.
associated with medical therapy approval should hopefully no longer represent a point of antagonism. In the case of Nusinersen, the adoption of a fairness framework may translate into malleable coverage determinations that can fluidly shift based on a combination of new and emerging evidence of clinical effectiveness, fluctuating drug pricing on the part of drug developers as more pressure is placed on them to leverage the Orphan Drug Act more appropriately, and ongoing patient advocacy.

THE MEDICAL FUTILITY FRAMEWORK

The adoption of an “accountability for reasonableness” approach by policymakers may not represent the most satisfying of conclusions in a long-held debate about the use of CEA in coverage decision contexts, but it at the very least provides a method of validation for its use in a moment when a focus on cost is undeniably necessary. For those decision-makers, however, who more so align themselves with the Kantian imperative and the notion of the ‘rule of rescue,’ it may be more comforting to look to medical futility versus CEA as a guide through which to justify their approval or disapproval of coverage for a given drug. In the case of the utilization of futility, “the central question is not ‘how much money does this treatment cost’ but instead, ‘does the intervention have any reasonable prospect of helping [the] patient.’” As will become clear in the paragraphs below, however, the use of medical futility as a primary decision-making framework presents as particularly challenging from an ethical perspective in the case of its application to Nusinersen.

“Medical futility” refers to an intervention that is unlikely to produce any significant benefit for the patient. The principle emerged in the 1980s and was borne out of a time in which there was a broad-based effort to “re-assert professional judgement...when patient autonomy had achieved primacy in ethics and law.” The rationale for the development of such a concept by those in the medical sphere rested on concerns that technological advancements in the field of medicine had

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57 Jecker N [Internet]. Medical Futility, Ethics in Medicine at the University of Washington School of Medicine; c2014 [cited 2018 Sept 21]. University of Washington School of Medicine. Available from: https://depts.washington.edu/bioethx/topics/futil.html
58 Ibid.
reached a point at which they were leading to the prolongation of the dying process for terminally ill patients while at the same time contributing to the “heavy burden of healthcare costs.” Moreover, it reflected a “perceived need by doctors to...justify...decision[s] not to provide life-sustaining treatment” in such contexts. This is not to say that since medical futility’s introduction into the bioethical lexicon, its application has not been fraught with ethical uncertainty and intense debate. Yet, it continues to be leveraged as a mechanism through which to make medical decisions for patients in critical states of health.

The key criticism that it has faced, however, is important to highlight in that it forms the basis for why Nusinersen, among some other new drugs for which coverage decisions must be made, is not easy to validate from a medical futility standpoint. Namely, this is due to the fact that “despite its air of objectivity, a determination that treatment is futile is subjective” given its definitional application. Physiological futility is objective in that it translates into a zero percent chance of effectiveness for a given patient. In this way, it is considered “the narrowest...and most clearly defined definition of medically inappropriate care.” But given that there is some proven efficacy to the drug as presented in its clinical trials, this is not the form of futility that is applicable in this scenario; it is, on the contrary, the much more so subjective variants of quantitative and qualitative futility that pertain. In their paper on Medical Futility—Who Decides?, Jecker and Pearlman distinguish between quantitative and qualitative futility, explaining that quantitative futility “focuses on the probability that a particular outcome can be achieved and involves the judgement that this probability falls below a threshold considered minimal.” They contrast this with the idea of qualitative futility, which addresses the quality of the benefit of a given intervention. In defining a concept of medical futility that encompasses both quantitative and qualitative components, they highlight the challenges inherent in assigning

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62 Ibid.
decision-making authority. On the one hand, they state that the quantitative judgements “rest squarely with physicians.” On the other, they note the complexity of delineating whose responsibility it is to deem an intervention qualitatively futile, as this aspect of futility encompasses a desire to avoid paternalism and promote individual quality of life. From their perspective, the qualitative component falls more so into the patient’s domain. And in the case of care delivery for a child, this conceptually extends into the parents’ domain according to the idea that “parents are the fiduciaries of their child who is a patient.”

As it applies to Nusinersen, addressing these two aspects of medical futility is particularly problematic as it relates to decision-making. This is because there is a lack of clarity in what defines quantitative futility for patients being administered the drug, thus swinging the pendulum much more so in favor of qualitative—and therefore largely patient and parent-oriented—decision-making power. First, the data provided to the FDA did not involve those patients with SMA types 3 and 4 for whom the drug was ultimately approved for administration, so we do not have a solid gauge for this subset of the disease population as to what constitutes treatment response. Second, the drug’s leading clinical trials defined treatment response itself (i.e. “≥2-point improvement in ability to kick (or maximal score), or ≥1-point improvement in any other milestone, excluding voluntary grasp” in ENDEAR for infantile-onset SMA), but did not clearly qualify a lack of response – as maintenance of motor milestones also contributed positively to secondary outcomes, such as “no death.” In his editorial on Nusinersen for Spinal Muscular Atrophy—Are We Paying Too Much For Too Little?, Vinay Prasad comments further on the fact that “‘responder’ is an arbitrarily dichotomized end point that does not capture the mean treatment effect.” This creates a scenario, therefore, in which is it perfectly justifiable, for example, for a patient able to maintain flexion and extension of the right arm in order to operate an electric wheelchair to continue receiving the drug if ongoing administration aligns with their personal goals and is a state deemed by the patient to not be qualitatively futile. The Spinraza

65 Ibid.
66 Ibid, 1142.
68 Kuntz, N. Phase 3 ENDEAR Study Assessing the Efficacy and Safety of Nusinersen in Infants With Spinal Muscular Atrophy (SMA). Presentation presented at: 69th Annual Meeting of the American Academy of Neurology; 2017 April 24; Boston, MA.
website for patients, which is set up to provide definitive information about the drug for possible utilizers, even plays to the strengths of this argument – featuring quotations by patients that highlight how the drug’s administration has allowed fulfillment of individual objectives in treatment. One patient on the site notes that in her decision-making to start therapy “daily activities were important to me, like brushing my hair, doing my makeup, or changing clothes on my own” (See Figure 3).

![Image of qualitative advertising on Nusinersen’s (Spinraza) website](https://www.spinraza.com/en_us/home/taking/dosing.html)

**Figure 3. Qualitative advertising on Nusinersen’s (Spinraza) website**

The difficulty in firmly defining what constitutes medical futility in the frame of Nusinersen also rests in the fact that there are no other mainstream gene-targeted biologics for neurodegenerative conditions currently on the market from which to glean clinical pearls. In fact, Eteplirsen for Duchenne Muscular Dystrophy, which was released virtually in parallel with Nusinersen, is bound to be similarly forced into a head-on confrontation with what constitutes valid drug coverage approval. And of the biologics that are currently on the market, the majority of outcome measures evaluated are much more binary than those presented in Nusinersen’s FDA application. For Gefitinib, an EGFR inhibitor approved for the treatment of non-small cell lung

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"Ibid."

cancer in 2003, resistance to therapy as defined by cancer progression (based on Response Evaluation in Solid Tumors) represents grounds for its withdrawal.\textsuperscript{73} For Lumacaftor/Ivacaftor (Orkambi), a combination Cystic Fibrosis drug released to market in 2015 that combines a protein folding chaperone and CFTR potentiator, a lack of improvement in respiratory status suggests treatment failure. The clarity with which determinations in both of these exemplars as to the efficacy of the drug leads to a much more facile determination of the notion of quantitative futility. This transparency does not exist in the case of Nusinersen.

Additionally, in their paper on \textit{The Ethics of Forgoing Life-Sustaining Treatment}, authors Welie and Have put forth the argument that “from an ethical perspective, the default is “do not treat.””\textsuperscript{75} They explain that this is chiefly linked to the challenges presented by the necessity of ensuring both a medical indication and a consent to start treatment…and likewise… [that the drug] is still medically indicated and the patient is continuing to consent to it [for its provision].”\textsuperscript{76} In the context of Nusinersen, the ability to ensure both of these stipulations is tenuous at best. Burgart et al have already highlighted the muddiness of consent in this instance given “the paucity of available results” and consequent contribution to “prognostic uncertainty.”\textsuperscript{77} And with regard to the addressing of “medical indication,” there appears to be no clear delineation between medical indication versus quantitative futility. Thus, futility, as noted above, is much more so outlined by a qualitative assessment, granting the patient the autonomy to decide on initiation and/or continuance of treatment—which is simply unsustainable given the exorbitant cost of the drug. Thus, for all of these reasons, decision-makers are forced to reject coverage on the basis of medical futility.


\textsuperscript{76} Ibid.

\textsuperscript{77} Burgart et al, 189.
CONCLUSION

In a recent analysis of payment breakdowns among patients receiving Nusinersen at Boston Children’s Hospital, roughly 10% of the non-foreign patient population receiving the medication had public insurance coverage, as compared with 90% of patients who had private insurers. If we extrapolate that this breakdown is similar to that of patient populations across the United States receiving the ASO therapy at other tertiary care facilities, we assume that roughly 10% of the SMA community now on the drug will be severely impacted by impending national Medicaid limitations. We are moving quickly into a scenario in which disparities in care will grow ever wider, and a patient’s ability to pay or not to pay will become the sole bargaining chip in determining whether or not they can acquire the drug. This is not a situation that we want to find ourselves in in the coming years. Further, the very high price tag of Nusinersen will likely force many private insurers to follow suit and begin to more universally scrutinize coverage decisions for Nusinersen. We must be prepared to anticipate the downstream effects of such by thoughtfully considering and providing practical insights into the ways in which the ethical frameworks of CEA and medical futility can and should be used.

The introduction of Nusinersen onto the market was not without ethical challenges on the part of payors, particularly given the need to weigh the drug’s cost against its efficacy, which was not strongly demonstrated in the initial clinical trial dataset submitted to the FDA by Biogen and Ionis. At the same time, however, the approval of the drug has instilled new optimism into a rare-disease community that has long suffered. We must, therefore, better establish the ethical underpinnings of the drug approval process—in so doing demanding a greater rigor to the proof of efficacy on the part of clinical trial data that would facilitate a more likely demonstration of cost-effectiveness and of quantitative futility—while at the same time continuing to advocate for the advancement of care for those that need it most.
BIBLIOGRAPHY


Jecker N [Internet]. Medical Futility, Ethics in Medicine at the University of Washington School of Medicine; c2014 [cited 2018 Sept 21]. University of Washington School of Medicine. Available from: https://depts.washington.edu/bioethx/topics/futil.html


Kuntz, N. Phase 3 ENDEAR Study Assessing the Efficacy and Safety of Nusinersen in Infants with Spinal Muscular Atrophy (SMA). Presentation presented at: 69th Annual Meeting of the American Academy of Neurology; 2017 April 24; Boston, MA.


U.S. Food and Drug Administration [Internet]. FDA approves first drug for spinal muscular atrophy; c2016 [cited 2018 Sept 21]. Available from: https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm534611.htm

