Re-Examining the Ethics of Clinical Trial Approval in a Gene-Targeted Era through a Case-Based Approach: Exploring the Implications of the *n* = 1 Batten Disease Trial

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ABSTRACT

Using a case-based approach, this article highlights the necessity of re-examining the ethics of clinical trial approval in a gene-targeted era. It centers on the *n* = 1 Batten disease drug trial, in which an antisense oligonucleotide drug was introduced as a novel drug therapy for an individual child with a neurodegenerative illness, and probes the ethics of equity, safety, clinical utility, and parental autonomy of the trial as a means to raise more global questions about the ethical underpinnings of clinical trail approval. With the promise of the widespread application of personalized medicine on the horizon, it is imperative that the greater scientific community think critically about the ethical foundation upon which drugs make their way to market.

For M.M.'s parents, there was nothing but excitement when they welcomed their first child in 2010. "When I think about [M.M.] as an infant, I think about smiles . . . and laughter . . . and health," her mother recalls.[1] When M.M. was a toddler, her father described her as being "very physical," noting that she "always loved to ride her Strider [rocking toy] . . . play in the snow . . . [and] go sledding," in their hometown in Colorado. Her parents had no sense early on that their daughter was in the throes of a serious neurodegenerative decline. But when M.M. turned three, subtle signs emerged that suggested otherwise.[2]

M.M. began to get "stuck on her words." She would stop mid-sentence, as if unable to complete her thoughts. Given that she had consistently met all of her developmental milestones up to that point, her medical care team was not initially concerned. But with each passing month, her behavior grew stranger, and her parents began to ask questions. By age four, M.M. started pulling books close to her face to make out the images. At five, she began moving her feet in an unusual "pit-patter" manner, repeatedly stumbling and falling. At six, M.M. displayed worsening gait, language, and behavioral regression, and a complete loss of vision. She was declining rapidly, and her doctors did not know why.[3]

An extensive evaluation performed at Children's Hospital Colorado in 2016 revealed multisystem deficits. M.M. was found to have severe vision loss, in association with bilateral macular and retinal dystrophy, and resultant trace optic disc pallor on the right. An electroencephalogram (EEG) showed severe bilateral cerebral dysfunction, with multifocal and generalized epileptiform discharges suggesting subclinical seizure activity. Magnetic resonance imaging (MRI) of her brain and spine revealed significant cerebellar atrophy. After an extensive molecular workup, an answer as to M.M.'s predicament

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emerged. It was the not the answer her parents had hoped to hear.[4]

M.M. was diagnosed with Batten disease, or neuronal ceroid lipofuscinosis, a rare, fatal, inherited condition caused by lysosomal accumulation of ceroid lipofuscin. Swaiman and colleagues explain that patients with the disease suffer from "cognitive impairment . . . [progressively] worsening seizures . . . [and] loss of sight and motor skills."[5] According to the National Institute of Neurological Disorders and Stroke, Batten disease affects two to four of every 100,000 live births in the United States, and about 14,000 children worldwide.[6] It has no definite cure.

M.M.'s parents were determined to change that—for their daughter and for all patients afflicted with the disease. Their first step was to clarify the genetic underpinnings of the disorder. M.M.'s original Batten gene panel was sent from Children's Hospital Colorado after a skin biopsy showed characteristic changes. The panel identified a heterozygous change in the CLN7 gene, which meant that there was a second gene at play in her disease. This was because the CLN7 disease variant of Batten disease is classically recessive, requiring a homozygous change in two alleles at the particular gene locus. Seeking more answers, M.M.'s parents forged a special partnership with Claritas Genomics, a diagnostic laboratory then associated with Boston Children's Hospital. Claritas offered to provide whole exome sequencing for M.M., with the hope that the second gene that contributed to her Batten disease presentation would come to light.

The results indicated that M.M.'s specific mutation was caused by a retrotransposon insertion in the CLN7 gene. Retrotransposons are components of the genome that utilize a "copy and paste" mechanism to insert to target gene sites, and are abundant in the DNA of eukaryotic organisms (organisms that include animals and plants). In M.M.'s case, the insertion was acting as an exon trap, in that it caused alternative splicing and consequent gene truncation and loss of protein function of the gene.

A new question arose as to how this newly identified genetic defect could be addressed in a therapeutic context. Timothy Yu, MD, PhD, a researcher affiliated with Boston Children's Hospital, proposed using the Claritas data to develop an oligonucleotide drug that would block the specific abnormal splicing process that was occurring in M.M.'s genome and restore the normal CLN7 gene product.[7]

This endeavor sought to capitalize on the recent successes of similar therapy approaches for other childhood diseases. Oligonucleotide drugs that target mRNA splicing mechanisms had recently been introduced. In December 2016, the U.S. Food and Drug Administration (FDA) approved nusinersen (Spinraza), an antisense oligonucleotide that was designed to alter irregular SMN2 splicing, the first definitive therapy for spinal muscular atrophy (SMA).[8] The drug had been accepted for FDA priority review in November 2016 "to address the urgent need for an effective SMA treatment" in light of the positive statistical data on improvement in motor milestones demonstrated in the drug's two Phase III studies (see table 1 for descriptions of the various phases in experimental drug trials).[9] In September 2016, the FDA approved the oligonucleotide drug eteplirsen (Exondys 51) for treatment of Duchenne muscular dystrophy, based on efficacy data collected from four different Phase I through Phase III trials that were conducted between January 2009 and September 2014.[10] The clinical trials for nusinersen and eteplirsen involved sample sizes far greater than what would be utilized in M.M.'s case, which would be a clinical trial with a research population of one subject: $n = 1$.

Yu agreed to lead the research efforts, and, faced with M.M.'s increasingly rapid neurologic decline, her parents launched an online advocacy platform to raise the million dollars necessary for undertaking the $n = 1$ clinical trial for their daughter, and to seek FDA approval for moving forward with the project. Within a few months, the idea for a new drug therapy had a fast-tracked timeline to begin a clinical trial.[11]

TABLE 1. Phase I - II - III versus $n = 1$ trial design

Phase	Sample size (n)	Length of phase	Purpose of phase
I	20 - 100	Several months	Safety (determination of doses tolerated without signficiant side-effects).
II	100 -1,000	Several months to ~ 2 years	Efficacy of varying safe dosages.
III	1,000+	1 to 4 years	Safety. Efficacy on a large scale.
I-II-III	1	Several months	Safety (determination of dosages tolerated without signficiant side-effects). Efficacy of varying safe dosages.

The development of the clinical trial broke new ground in numerous ways, not only due to its highly accelerated timeline, but also due to its sample size. As a trial initiated for an individual, there was an inherent blurring of the classic structure of the phases of clinical trials, in which periods of active treatment with an experimental drug are followed by "washout" periods, when the experimental drug is "washed out" of the system of research subjects. In the Batten disease trial, the safety of various dosages of the experimental drug would be monitored alongside the efficacy of the drug over the period of a few short months. In the usual structure of a clinical trial for an experimental drug that involves human subjects, a small research population (usually fewer than 100 people) participates in Phase I of the trial, and the subjects are carefully monitored for side-effects at a range of drug dosages over a period of several months (see table 1.) In Phase II of the trial, hundreds of human subjects are strictly monitored to assess the efficacy of the experimental drug at varying "safe" dosages over a period of months to a period of two years. Significantly larger cohorts participate in Phase III of the trial, in which data are collected regarding the safety and efficacy of the drug over a period of one to four years, utilizing the dosage information that was acquired in Phase II.

The stark contrasts between the design of the $n = 1$ trial and that of traditional Phase I, Phase II, and Phase III trials indicate the need to develop and/or, at the very least, reexamine the ethical framework for approving clinical trials with human subjects, especially as gene-targeted therapies overtake nontargeted therapies. In 1966, Henry Knowles Beecher published his seminal work "Ethics and Clinical Research" in the *New England Journal of Medicine*, in which he urged the scientific community at large to adopt a significantly more stringent ethical standard for scientific experimentation involving human subjects, and shed light on what he deemed "troubling practices" in the U.S.[12] This occurred on a backdrop of an already evolving federal framework that regulated how new drugs were brought to market, but it was Beecher's resolve that ultimately paved the way for the development of the carefully designed I-II-III phase system for clinical trials by as early as the 1970s. As widespread personalized medicine is imminently on the horizon, the ubiquitous use of the $n = 1$ trial design will require a reconsideration of the ethical principles on which Beecher's imperatives rested. The remainder of this article will consider the significance of the Batten disease trial in the larger context of clinical trials, with an examination of the key ethical principles of equity, clinical utility, safety, and parental autonomy.

EQUITY

Massive budget cuts to the U.S. National Institutes of Health (NIH) proposed by the Trump administration in March 2017 threaten to reduce NIH's funding by roughly six billion dollars, and continued monetary provisions for biomedical research are at risk.[13] Particularly at risk are funds for orphan diseases, defined as "a rare disease or condition . . . that affects less than 200,000 persons in the US."[14]

The Orphan Drug Act (1983), however, has functioned for more than 30 years to help offset the costs of drug-related research for rare diseases. This legislation comes from an era in when the costs of drug research skyrocketed in response to the increased safety and efficacy data required for the approval of new drugs. The Kefauver-Harris Amendment of 1962 was the U.S. response to the drug thalidomide's highly publicized role in contributing to defects in human embryonic development.[15] As a result of the 1962 ruling, independent researchers and pharmaceutical companies were required to comply with significantly more stringent guidelines to get new drugs to market. Cost effectiveness became an even more important factor in the pharmaceutical industry's selection of projects to pursue, and rare diseases were progressively cast to the side. Patients with rare diseases and their families banded together to form the National Organization for Rare Disorders (NORD) in 1982, an advocacy organization that was instrumental in the passing of what ultimately became the Orphan Drug Act of 1983.[16]

The Orphan Drug Act facilitated the revitalization of drug research for rare diseases in a number of ways. The act provided seven years of market of exclusivity for companies that developed a drug to treat a rare disorder, which limited competition and allowed a window of profitability. It offered exemptions from certain FDA fees, tax credits for various research-related expenditures, and governmental aid for research.[17]

These federal policies supporting drug research for rare diseases help to counterbalance the high cost of developing treatments for the diseases. The concept of equity, as outlined below, plays a significant role in solidifying governmental support of the development of treatments for rare diseases. In some ways, M.M.'s drug trial raises questions about the durability of that justification.

The current policy-influencing stance on equity centers on a rights-based approach, which is derived

from a notion of "natural rights" put forth by the 17th century philosopher and physician John Locke.[18] Hughes, Tunnage, and Yeo argue that a rights-based approach to healthcare is grounded in the idea that "individuals in a society are entitled to a decent minimum of health care . . . [and are deserving of] the same quality of treatment as other patients."[19] This is juxtaposed with a consequentialist view of equity, which contends that, as a society, we are obligated to make decisions that center on "bringing the greatest good to the greatest number."[20] The rights-based argument is supported by the concepts of "fair innings" and the "rule of rescue."[21] In his article "Intergenerational Equity," Williams defines the concept of "fair innings" as the "feeling that everyone is entitled to some 'normal' span of health."[22] Jonsen, in his seminal article "Bentham in a Box: Technology and Healthcare Allocation," defines the "rule of rescue" as "a perceived duty to save endangered life where possible."[23] The "duty" Jonsen refers to highlights the influence of the Kantian imperative for beneficence, in that it underscores the obligation of a civil society to protect the most vulnerable and to uphold the collective morality of its citizens.[24]

The equity arguments that support the Orphan Drug Act are problematic when applied to the clinical trial approved for the oligonucleotide drug designed for M.M., due to the neurodegenerative aspects of her disease. Williams's "fair innings" argument includes the notion of a " 'normal' span of health," but this is a challenging concept in the context of M.M.'s illness, which had already caused significant neurodegenerative decline. The drug promised to restore the gene product so as to prevent further neurologic change, but there was no likely component of reversibility.[25] There are also questions regarding the validity of an equity-based position; from the standpoint Jonsen's "rule of rescue," this concept is applicable when an individual faces "a real threat of avoidable death."[26] But can neurodegeneration be equated with "avoidable death" here?

Thus, rights-based equity arguments do not provide strong ethical support for the Batten disease trial. Approval of the trial also does not appear to be sound from a consequentialist approach to equity and/or a look to cost effectiveness. A consequentialist approach (that is, an approach that holds that what is right or best is what makes the world better in the future) would be valid, however, in the context of an $n = 1$ trial as a "proof of concept," in which the trial itself could prove (or disprove) that the approach proposed by the researchers has widespread downstream applicability. Hughes argues that the broader societal implications fostered by data that are collected from a trial on an individual could be argument enough to satisfy the requirement of delivering "the greatest good to the greatest number."[27] But in the case of this trial, there was a lack of novelty—and consequently a lack of "proof of concept"—because the FDA had already approved nusinersen and eteplersin in the market of antisense oligonucleotide as exon-skipping therapy.

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The neurodegenerative aspects of M.M.'s disease and the lack of "proof of concept" for the $n = 1$ trial do not provide an ethical justification for the trial based on the principle of equity. More generally, the trial provides fodder for a broader discussion of the definition of "orphan disease," as disease processes will increasingly be identified by the gene mutations that create them. If an "orphan disease" is defined as one that affects 200,000 or fewer individuals in the U.S., how will new subsets of more common diseases be identified as they emerge? Where will the line be drawn when resources for the development of new drug therapies are allocated? Who will draw these lines, as new federal guidelines permit the chairs of institutional review boards (IRBs) to approve $n = 1$ trials for novel therapies without the standard review process, thereby bypassing the committee and its deliberations?[28] Such expedited review may eliminate the community voice and suppress the ability of the public to have a stake in determining how governmental dollars are spent.

There may be a point at which leveraging the notion of equity will be become unsustainable, monetarily and otherwise.

CLINICAL UTILITY

The question of equity is relevant within the frame of clinical utility, as a clinical trial that may result in a widely beneficial treatment may be easier to support than a trial that offers the possibility of a more limited treatment. For example, if M.M.'s $n = 1$ trial was the first antisense oligonucleotide (ASO) drug, it could serve as a catalyst in the arena of ASO drug development. This was not the case, however, as nusinersen and eteplirsen had already been brought to market.

The clinical utility of M.M.'s $n = 1$ trial was under scrutiny due to its small sample size. Halpern, Karlawish, and Berlin argue in "The Continuing Unethical Conduct of Underpowered Clinical Trials" that underpowered trials for rare diseases are not ethically justified unless "investigators document explicit plans for including their results with those of similar trials in a prospective meta-analysis."[29] But it was not realistic to expect that the drug designed specifically for M.M.'s CLN7 mutation—a small, perhaps unique, subset of mutations causing Batten disease—could be incorporated into a prospective meta-analysis. And in conjunction with this, from an analysis standpoint, the $n = 1$ design of M.M.'s trial introduced additional challenges; there is little research regarding the appropriate assessment of $n = 1$ trial data. As Lillie and colleagues note, even though "washout" periods are intended to mitigate the effects of prior interventions, "accounting for carryover effects is not trivial," and these periods may serve as a barrier to producing data that can be extrapolated for use in other contexts.[30] This may further complicate the incorporation of data collected from M.M.'s trial into a larger analysis pool, whatever that may be.

Other ethicists have offered different perspectives on the ethical justification of underpowered trials. In their article published in *Lancet,* "Why Underpowered Trials Are Not Necessarily Unethical," Edwards, Lilford, Braunholtz, and Jackson maintain that equipoised trials ought to be "acceptable to both [conquentialists], who are concerned simply to achieve the most good, and to non-[consequentialists], who are concerned that the interests of future patients generally should not be allowed to override the rights of present patients."[31] (The term "equipoised" refers to *clinical equipoise*—the ethical basis for the conduct of randomized clinical trials involving human subjects—in which there is uncertainty regarding which arm of the clinical trial is therapeutically better than the other.)

For M.M.'s trial, could it have been anticipated that the new drug treatment would be better than no treatment at all? Was the halting of disease progression without the promise of reversibility argument enough for implementation of the trial? This most likely is not the equipoise upon which the above authors sought justification.

SAFETY

A determination of clinical equipoise, necessary for the FDA approval of a new drug protocol, includes analysis of the risks and benefits to patients and the safety of the experimental drug at the time of its administration. The safety of antisense oligonucleotide drugs is well documented in the literature.[32] Chan, Lim, and Wong note that much of the data collected thus far indicates that the majority of "toxic effects are dependent on the ASO backbone chemistry . . . [and are] sequence independent."[33] The most significant toxicities derived from multiple studies include complement and coagulation cascade activation, thrombocytopenia, hyperglycemia, and hypotension. Many of the effects have been associated with dose-dependence, and could therefore be mitigated by lowering doses.[34]

Despite the generally sequence-independent nature of the identified toxicities, it is important to consider each ASO drug as a new compound when reviewing its safety data, given the specific targeting of distinct gene exons. Wilton and colleagues found that although "the possibility of off-target annealing" is probabilistically low, it remains a risk.[35] In the most recent safety review application released for the SMA drug nusinersen (Spinraza), for example, the data suggest the drug contributes to inducing thrombocytopenia (in five of 56 of patients), proteinuria (in 33 percent of patients with infantile-type SMA and in 69 percent of patients with later-onset SMA and longer duration of treatment); hyponatremia (severe in one patient); decreased growth; rash (in two of 173 patients); and possible vasculitis (one patient).[36] Yasuda and colleagues reported to the FDA that while there is an overlap with the toxicities identified in other ASO studies, new drug-specific toxicities are also apparent. Further, the overarching safety analysis underscores the very real possibility that more significant toxicities will reveal themselves in the future. Yasuda and colleagues note: "The magnitude of the potential for serious harm after approval is unknown. Because

of limitations due to the small number of patients exposed and duration of exposure in the clinical trials, it is likely that adverse reactions not identified to date, or of a magnitude not observed to date, will occur in the postmarketing setting."[37]

Thus, the fast-tracking of an experimental drug through a clinical trial, coupled with a small population size, may limit the perceptibility of adverse effects. This has explicit relevance to M.M.'s trial, for which the Orphan Drug Act facilitated a similarly accelerated clinical trial approval process and for which the sample size was even smaller. If toxicities reveal themselves downstream—primarily in a postmarketing context—will it be necessary to rethink the existing framework of drug safety monitoring and regulation overall? Will there be the monetary and staff-based wherewithal to ramp up widespread post-market analysis?

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The ethical conundrum posed in the context of drug safety for this experimental treatment also centered on the challenges introduced by the $n = 1$ study population. In M.M.'s case, these challenges were largely based on her age and her specific neurodegenerative condition. In "Research Ethics and *N*-of-1 Trials," Crowden, Guyatt, Stepanov, and Vorhra argue that when "*N*-of-1 trials are undertaken as part of clinical care . . . the clinician and patient enter a partnership."[38] It is through this partnership that treatment targets are monitored. In addition to concrete health data, this system relies heavily on patient-reported symptoms. But M.M.'s ability to communicate was limited by her age and her disease process. Given this, was it possible that M.M. could have entered this partnership fairly? To what extent could the patient have accurately self-advocated with regard to monitoring treatment targets and symptoms? Could M.M.'s parents have served as appropriate stand-in spokespersons for her?

PARENTAL AUTONOMY

Donovan and Pelligrino note that "parental preferences may or may not reflect the good of the child." They state, "although we act as if a suitable proxy can exercise the autonomy of the nonautonomous child, this is not altogether an unreasonable fiction."[39] This is why, in defining autonomy as it pertains to decision making for a child, McCullough describes the necessity of recognizing the "pediatrician and parents . . . [as] co-fiduciaries of the child who is the patient."[40] He underscores the role of the physician in guiding the decision-making process, serving as a trusted clinical expert and source of scientifically rooted judgment.

With regard to M.M.'s trial, we would like to assume that her parents acted as a "suitable proxy" when they gave permission for her to participate in the experimental drug trial. Numerous studies have questioned the ethical nature of the consent process as it pertains to clinical trials involving children—perhaps making the entire enrollment process unethical, particularly without the clear directorial role of the child's physician as co-fiduciary. In "Parental Perceptions and Attitudes about Informed Consent in Clinical Research Involving Children," Harth and Thong present what they call "worrisome" data regarding parental naiveté surrounding their comprehension about their child's participation in a clinical trial.[41] Harth and Thong argue that, in the majority of cases, most parents do not have a solid understanding that drug trials examine the efficacy and safety of a treatment at different times. The authors also identify a lack of parental awareness regarding the general risks involved in participation of a clinical trial, and a parents' lack of a fundamental understanding about the consent document's role in helping "protect their rights . . . [and allowing them to] withdraw their child unconditionally from the trial at any time [if desired]."[42] Barfield and Church, in "Informed Consent in Pediatric Clinical Trials," draw attention to the notion that many parents who give consent for their child to participate in a clinical trial do not understand the basic tenets of trial design such as randomization or the differences between the clinical phases (see table 1).[43] In an analysis of informed consent processes for an oncologic

randomized controlled trial (RCT) among pediatric and adult populations, Simon and colleagues found that the adult oncologic patients were "more fully informed and more actively engaged by their oncologists" than the pediatric surrogate decision makers were.[44] The authors found that 92.5 percent of the adult patients accurately identified the implications of randomization in the selection of treatment options in the clinical trial, versus 40 percent of the pediatric surrogates. Six to eight months after the beginning of the trial, the pediatric surrogates reported a much higher, statistically significant, overall level of regret about the decision to participate in research than the adult subjects did ($p = .002$). Interestingly, Simon and colleagues found that the adult subjects indicated a much higher baseline level of trust in their oncologist compared with the pediatric surrogates.[45]

In "Two Concepts of Clinical Optimism," Jansen considers the role of therapeutic optimism on the ethical validity of the consent process in clinical trials involving children.[46] Jansen distinguishes dispositional optimism from unrealistic therapeutic optimism, and explains that unrealistic therapeutic optimism may impair parents' ability to ethically provide consent for their child to participate in a clinical trial. In Jansen's view, dispositional optimism is "ethically always tolerable because hope does not compromise autonomy of a decision to participate in research."[47] She contrasts this with unrealistic therapeutic optimism, which is a "hope for an unlikely cure . . . [that] can reduce participants' autonomy" through its "overestimate[ion] of the likelihood or magnitude of medical benefit."[48] What was the nature of M.M.'s parents' optimism for M.M.'s trial? Was it unrealistic? If so, was their proxy decision making unethical? As previously noted, there was uncertainty as to how much the drug could contribute to neurocognitive reversal in M.M.'s case. It was more realistic to think that it would halt further neurodegeneration, leading to questions regarding M.M.'s quality of life following the clinical trial, given her continued impairment.

CONCLUSION

Thus, from the perspectives of equity, clinical utility, safety, and parental autonomy, it seems that the FDA's fast-tracking and ultimate granting of approval for M.M.'s clinical trial may have been ethically unjustified—or at least ethically tenuous. While many of the arguments put forth and many of the questions raised in this article were driven by M.M.'s specific neurodegenerative process and her young age, the emphasis on reassessment of clinical trial approval from numerous ethical standpoints is warranted more generally as we move into an era of gene-targeted treatments, in which the possibility of individualized drug development becomes a reality. The principle of distributive justice will take on greater importance in a heavily budget-constrained context, as will the necessity to derive clinical utility from $n = 1$ studies, and the need to appropriately monitor drug safety. Emerging studies with children will need to be evaluated much more systematically for the reliability of consent made by surrogate decision makers. Upholding these ethical standards will allow us to facilitate and propel therapeutic advancement.

PRIVACY

To protect her privacy, the patient's name has been changed to "M.M."

NOTES

1. The patient's name and situation have been extensively discussed by her parents in the press and online. G. Kolata, "Drug Designed for One Raises Many Questions," *New York Times* 15 October 2019; published online as G. Kolata, "Scientists Designed a Drug for Just One Patient. Her Name is Mila," *https://www.nytimes.com/2019/10/09/health/mila-makovec-drug.html;* J. Vitarello, "Saving Mila—Time is Running Out!" 16 December 2016, *https://www.youtube.com/watch?v=Rt8aJuOLvZE.*

2. Vitarello, "Saving Mila," ibid.

3. Ibid.

4. M. Keshavan, "Saving Mila: How a tailor-made therapy, developed in a flash, may have halted a young girl's rare disease," *STAT Reports,* 22 October 2018, *https://www.statnews.com/2018/10/22/a-tailor-made-therapy-may-have-halted-a-rare-disease/.*

5. K.F. Swaiman et al., *Swaiman's Pediatric Neurology: Principles and Practice* (Edinburgh, Scotland: Elsevier, 2017) p. 974

6. U.S. National Institutes of Health, National Institute of Neurological Disorders and Stroke, U.S. Department of Health and Human Services, "Batten Disease Fact Sheet," 13 March 2020, *https://www.ninds.nih.gov/Disorders/Patient-Caregiver-Education/Fact-Sheets/Batten-Disease-Fact-Sheet.*

7. Keshavan, "Saving Mila," see note 4 above.

8. T. Cooper, "Biogen's Regulatory Applications for Nusinersen as a Treatment for Spinal Muscular Atrophy Accepted by FDA and EMA," *Business Wire,* 28 October 2016, *http://www.businesswire.com/news/home/20161028005104/en/Biogen%E2%80%99s-Regulatory-Applications-Nusinersen-Treatment-Spinal-Muscular.*

9. Ibid.

10. K.R. Lim, R. Maruyama, and T. Yokota, "Eteplirsen in the treatment of Duchenne muscular dystrophy," *Drug*

Design, Development and Therapy 11 (2017): 533-45, doi:10.2147/dddt.s97635.

11. Keshavan, "Saving Mila," see note 4 above.

12. H.K. Beecher, "Ethics and Clinical Research," *New England Journal of Medicine* 274 (1966): 1354-60, doi: 10.1056/NEJM196606162742405

13. A. Kodjak and R. Stein, "Medical Research, Health Care Face Deep Cuts in Trump Budget," 23 May 2017, *https://www.npr.org/sections/health-shots/2017/05/23/529654114/medical-research-health-care-face-deep-cuts-in-trump-budget.*

14. U.S. Food and Drug Administration, "Developing Products for Rare Diseases & Conditions," 20 December 2018, *https://www.fda.gov/industry/developing-products-rare-diseases-conditions.*

15. U.S. Food and Drug Administration, "Kefauver-Harris Amendents Revolutionized Drug Development," 10 September 2012, *https://www.fda.gov/consumers/consumer-updates/kefauver-harris-amendments-revolutionized-drug-development.*

16. NORD, 2020, *https://rarediseases.org/about/what-we-do/history-leadership/.*

17. M.J. Field and T.F. Boat, "Summary," in *Rare Diseases and Orphan Products: Accelerating Research and Development* (Washington, D.C.: National Academies Press, 2010), doi: 10.17226/12953.

18. J. Locke, *Two Treatises of Government,* 2nd ed., ed. P. Laslett (Cambridge, U.K.: Cambridge University Press, 1967).

19. D. Hughes, B. Tunnage, and S. Yeo, "Drugs for exceptionally rare diseases: Do they deserve special status for funding?" *QJM: An International Journal of Medicine* 98, no. 11 (2005): 829-36, doi:10.1093/qjmed/hci128

20. D. Hughes, "Rationing of Drugs for Rare Diseases," *PharmacoEconomics* 24, no. 4 (2006): 315-6, doi:10.2165/00019053-200624040-00001.

21. A. Williams, "Intergenerational Equity: An Exploration of the 'Fair Innings' Argument," *Health Economics* 6, no. 2 (1997): 117-32, *https://onlinelibrary.wiley.com/doi/abs/10.1002/%28SICI%291099-1050%28199703%296%3A2%3C117%3A%3AAID-HEC256%3E3.0.CO%3B2-B.*

22. Ibid.

23. A.R. Jonsen, "Bentham in a Box: Technology and Healthcare Allocation," *Journal of Law, Medicine & Ethics* 14, no. 3-4 (September 1986): 172-4, *https://www.academia.edu/1210649/3._Bentham_in_a_Box_Technology_Assessment_and_Health_Care_Allocation*; F. Bochner et al., "Controversies in treatment: How can hospitals ration drugs?*" British Medical Journal* 308, no. 6933 (1984): 901-5, 907-8, doi: 10.1136/bmj.308.6933.901.

24. I. Kant, *Ethical Philosophy,* 2nd ed., trans. J. W. Ellington (Indianapolis, Ind.: Hackett, 1994).

25. Keshavan, "Saving Mila," see note 4 above.

26. J. Mckie and J. Richardson, "The Rule of Rescue," *Social Science & Medicine* 56, no. 12 (2003): 2407-19, doi:10.1016/s0277-9536(02): 00244-7.

27. Hughes, "Rationing of Drugs for Rare Diseases,"see note 20 above, p. 315.

28. "Food and Drug Administration Safety and Innovation Act," 9 July 2012, *https://www.congress.gov/112/plaws/publ144/PLAW-112publ144.pdf.*

29. S.D. Halpern, "The Continuing Unethical Conduct of Underpowered Clinical Trials." *American Journal of Medicine* 288, no. 3 (2002): 358, doi:10.1001/jama.288.3.358.

30. E.O. Lillie et al., "The n-of-1 clinical trial: the ultimate strategy for individualizing medicine?" *Personalized Medicine* 8, no. 2 (2011): 161-73, doi:10.2217/pme.11.7.

31. S. Edwards, R. Lilford, D. Braunholtz, and J. Jackson, "Why 'underpowered' trials are not necessarily unethical," *Lancet* 350, no. 9080 (1997): 804-7, doi:10.1016/s0140-6736(97)02290-3.

32. R.A. Smith et al., "Antisense oligonucleotide therapy for neurodegenerative disease," *Journal of Clinical Investigation* 116, no. 8 (2006): 2290-6, doi:10.1172/JCI25424.

33. J. Chan, S. Lim, and F. Wong, "Antisense Oligonucleotides: From design to therapeutic application," *Clinical and Experimental Pharmacology and Physiology* 33 (2006): 533-40, doi: 10.1111/j.1440-1681.2006.04403.x.

34. T.L. Jason, J. Koropatnick, and R.W. Berg, "Toxicology of antisense therapeutics," *Toxicology and Applied Pharmacology* 201, no. 1 (2004): 66-83, doi:10.1016/j.taap.2004.04.017.

35. S.D. Wilton et al., "Antisense Oligonucleotide-induced Exon Skipping Across the Human Dystrophin Gene Transcript," *Molecular Therapy* 15, no. 7 (2008): 1288-96, doi:10.1038/sj.mt.6300095.

36. S.U. Yasuda, "U.S. Food and Drug Administration, Safety Team Leader Review: New Drug Application 209531 Spinraza (nusinersen) Center for Drug Evaluation and Research Application Number 209531Orig1s000 Medical Review(s), 17 December 2017," *https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/209531Orig1s000MedR.pdf.*

37. Ibid.

38. A. Crowden, G. Guyatt, N. Stepanov, and S. Vohra, "Research Ethics and N-of-1 Trials," in *Essential Guide to N-of-1 Trials in Health,* ed. J. Nikles and G. Mitchell (Dordrecht, Switzerland: Springer, 2015), 125-33, doi: 10.1007/978-94-017-7200-6_11.

39. K. Donovan and E.D. Pellegrino, "Virtues and Goals in Pediatrics," in *Pediatric Bioethics*, ed. G. Miller (Cambridge: Cambridge University Press, 2010), 7-8.

40. L.B McCullough, "Pediatricians and Parents as Cofiduciaries of Pediatric Patients," in *Pediatric Bioethics,* ed. G. Miller (Cambridge, U.K.: Cambridge University Press, 2010), 18.

41. S. Harth and Y. Thong, "Parental perceptions and attitudes about informed consent in clinical research involving children," *Social Science & Medicine* 41, no. 12 (1995): 1573-7, doi:10.1016/0277-9536(95)00058-f.

42. Ibid., 1573.

43. R.C. Barfield and C. Church, "Informed consent in pediatric clinical trials," *Current Opinion in Pediatrics* 17, no. 1 (2005): 20-4, doi:10.1097/01.mop.0000145718.77939.b1.

44. C.M. Simon, L.A. Siminoff, E.D. Kodish, and C.

Burant, "Comparison of the Informed Consent Process for Randomized Clinical Trials in Pediatric and Adult Oncology," *Journal of Clinical Oncology* 22, no. 13 (2004): 2708-17, doi:10.1200/jco.2004.10.034.

45. Ibid.

46. L.A. Jansen, "Two concepts of therapeutic optimism," *Journal of Medical Ethics* 37, no. 9 (2011): 563-6, doi:10.1136/jme.2010.038943.

47. Ibid., 567.

48. Ibid., 568.