When Ethics Constrains Clinical Research: Trial Design of Control Arms in “Greater Than Minimal Risk” Pediatric Trials

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Abstract

For more than three decades clinical research in the United States has been explicitly guided by the idea that ethical considerations must be central to research design and practice. In spite of the centrality of this idea, attempting to balance the sometimes conflicting values of advancing scientific knowledge and protecting human subjects continues to pose challenges. Possible conflicts between the standards of scientific research and those of ethics are particularly salient in relation to trial design. Specifically, the choice of a control arm is an aspect of trial design in which ethical and scientific issues are deeply entwined. Although ethical quandaries related to the choice of control arms may arise when conducting any type of clinical trials, they are conspicuous in early phase gene transfer trials that involve highly novel approaches and surgical procedures and have children as the research subjects. Because of children's and their parents' vulnerabilities, in trials that investigate therapies for fatal, rare diseases affecting minors, the scientific and ethical concerns related to choosing appropriate controls are particularly significant. In this paper we use direct gene transfer to the central nervous system to treat late infantile neuronal ceroid lipofuscinosis to illustrate some of these ethical issues and explore possible solutions to real and apparent conflicts between scientific and ethical considerations.

Introduction

FOR MORE THAN THREE DECADES clinical research in the United States has been explicitly guided by the idea that ethical considerations must be central to research design and practice (NCPHSBRR, 1979). In spite of the centrality of this idea, attempting to balance the sometimes conflicting values of advancing scientific knowledge and protecting human subjects continues to pose challenges. Ensuring that risks are commensurate with potential benefits, that subjects are adequately informed and give appropriate consent, that they are not unduly induced to participate in research, and that private health information is adequately protected can at times present obstacles to conducting socially valuable and scientifically valid research (Kulynych and Korn, 2002; Bentley and Thacker, 2004; Orentlicher, 2005; Martin and Robert, 2007; Caplan, 2008).

Possible conflicts between the standards of scientific research and those of ethics are particularly salient in relation to trial design. Specifically, the choice of a control arm is an aspect of trial design in which ethical and scientific issues are

deeply entwined. Indeed, the interrelation between ethics and science when conducting clinical trials is illustrated by the general agreement that in order to be ethical, clinical trials must also be scientifically valid; otherwise, the exposure of human beings to risk cannot be justified (Emanuel *et al.*, 2000). To meet this standard, investigators must pay careful attention to the validity of the methods they use, have an appropriate design, verify that the questions they ask cannot be answered using animal models or *in vitro* methods, and have robust, relevant end points that are clearly defined to address discrete scientific problems.

For many clinical trials, what are thought to be the highest scientific standards can be followed without any conflict with the ethical requirements to minimize risks and to balance the risks to subjects with direct benefits to them and to society. For instance, in general, there is little disagreement that randomized, double-blind, placebo-controlled studies can be both scientifically and ethically sound when dealing with nonfatal conditions for which no proven effective therapy exists (Freedman *et al.*, 1996; WMO, 2000; Emanuel and Miller, 2001).

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There are, however, some cases where the requirements of appropriate control arms to ensure generally accepted scientific designs might clash with those of ethics. Although ethical quandaries related to the choice of control arms may arise when conducting any type of clinical trial, they are conspicuous in early phase gene transfer trials that are associated with significant risk and even death, involve highly novel approaches and surgical procedures, and have children as research subjects (Janson *et al.*, 2002; Worgall *et al.*, 2008; Souweidane *et al.*, 2010). Because of children's and their parents' vulnerabilities (Kipnis, 2003; Arkin *et al.*, 2005; Shilling and Young, 2009), in trials that investigate therapies for fatal, rare diseases affecting minors, the scientific and ethical concerns related to choosing appropriate controls are particularly significant. In what follows, we use direct gene transfer to the central nervous system (CNS) to treat late infantile neuronal ceroid lipofuscinosis (LINCL) to illustrate some of these ethical issues and explore possible solutions to real and apparent conflicts between scientific and ethical considerations in designing the control arms of risky clinical trials involving pediatric populations.

CNS Gene Transfer for LINCL

LINCL is an autosomal recessive lysosomal storage disease that primarily affects the brain and retina (Weleber, 1998; Williams *et al.*, 1999; Haltia, 2003; Worgall *et al.*, 2007). It is caused by mutations in the CLN2 gene, resulting in deficiency of the protein tripeptidyl peptidase I (TPP-I), a protease that functions to clip the C-terminal end of proteins (Vines and Warburton, 1999). The LINCL phenotype is inevitably fatal in childhood following progressive degenerative neurologic deterioration. The disease manifests between the ages of 2 and 4 years with seizures, ataxia, myoclonus, impaired vision, and delayed speech as the primary symptoms. Afflicted children develop blindness and lose mobility by the age of 4 to 6 years. Toward the late stages of the disease, feeding becomes difficult, resulting in poor weight gain. Death occurs by the age of 8 to 12 years. (Williams *et al.*, 1999; Mole and Williams, 2001; Haltia, 2003; Worgall *et al.*, 2007). There is currently no treatment for LINCL other than management of symptoms. The disease is rare, affecting 0.36 to 0.46 per 100,000 live births. In the United States there are 350 to 400 children at any one time with the disease (Wisniewski *et al.*, 2001; Crystal *et al.*, 2004).

Preclinical and clinical studies have shown the feasibility and initial promise of using an adeno-associated virus (AAV) to transfer the human CLN2 cDNA to the brains of children with LINCL (Crystal *et al.*, 2004; Hackett *et al.*, 2005; Sondhi *et al.*, 2005, 2007; Passini *et al.*, 2006; Worgall *et al.*, 2008; Souweidane *et al.*, 2010). Preclinical studies with rodents showed that administration of the human CLN2 cDNA by means of an AAV2-based vector (AAV2 hCLN2) was associated with a decrease in the abnormal accumulation of storage material in CNS neurons (Hackett *et al.*, 2005; Sondhi *et al.*, 2005; Passini *et al.*, 2006). This was followed by a clinical study in which the AAV2hCLN2 vector was administered directly to the CNS of 10 children with LINCL of severe or moderate severity in a neurosurgical procedure involving six burr holes, catheter insertion, and infusion of the vector in a total of 12 sites over several hours (Worgall *et al.*, 2008; Souweidane *et al.*, 2010). With the caveat that the

controls were five untreated children followed over time, but were not randomized or matched for genotype or clinical characteristics, the data suggested a reduced rate of neurological decline in treated children (Worgall *et al.*, 2008). Based on these data, further studies with children affected by the disease thus seem to be appropriate. But how do science and ethics interact in the choosing of a control arm to assess the safety and efficacy of gene therapy for LINCL?

Design of Control Arms for Clinical Studies

From a purely scientific perspective, well-designed, randomized, placebo-controlled trials (RCTs) are considered the gold standard for assessing the efficacy of new interventions (Sackett *et al.*, 1996; Meldrum, 2000). Indeed, some argue that RCTs provide the most objective, legitimate, and genuinely scientific evidence about the effectiveness of any medical procedure (Guyatt *et al.*, 2000; Devereaux and Yusuf, 2003). Hence, even when there is a clear recognition of the challenges that randomized clinical trials would impose on the development of drugs for rare, fatal diseases, and even when other trial designs are thought to be necessary in order to allow for needed medicines (Buckley, 2008; Griggs *et al.*, 2009; Mitsumoto *et al.*, 2009; Anonymous, 2010), the general agreement is that randomized clinical trials would provide the best evidence. But, as we show below, such belief is problematic.

RCTs require the selection of an appropriate control arm. In the case of a gene transfer trial for LINCL this would entail randomly assigning adequately matched affected children to either the experimental or the placebo-controlled group. Because the disease is global throughout the brain, it requires that the gene transfer be provided to as large a proportion of the CNS as possible. Hence, in order to provide intracranial, direct CNS administration, the delivery of the vector is performed through burr holes in each child's skull with general anesthesia over several hours. Thus, a placebo group would involve a sham surgery performed under general anesthesia. This group could then receive either a null virus vector or a saline injection in a double-blinded fashion, or sham surgery with no infusion and a single blind. Presumably, the most scientifically rigorous controlled study would include a blinded, randomized study with two arms: sham surgery with administration of a null virus vector versus surgery with the CLN2 coding vector.

In gene transfer trials for LINCL, however, following what is thought to be the highest standard of scientific evidence might conflict with ethical requirements to protect human subjects, which in this case are children. In particular, two interrelated aspects of RCTs raise ethical concerns: placebo use—which in this case would involve a sham surgery with administration of a null vector—and random allocation to the experimental or the placebo arm.

Placebo use

The ethical use of placebos in risky clinical trials is a matter of heated controversy (Macklin, 1999; Weijer, 2002; Horng and Miller, 2002; London and Kadane, 2002; Miller, 2003; Polgar and Ng, 2005). Because of their inability to fully participate in making autonomous choices, when the research subjects are children the use of placebos raises even more ethical concerns (Flynn, 2003; Miller *et al.*, 2003; Derivan *et al.*, 2004; Lynch, 2007; Martin and Robert, 2007; Morton, 2008). Nonetheless, even if one accepts that placebo

trials in general, and sham surgeries in particular, are sometimes ethically justified, the question still remains of when they are so.

Generally, placebo controls are thought to be ethically justifiable when they are supported by both sound methodological and ethical considerations (Emanuel and Miller, 2001; Miller and Brody, 2002). The existence of compelling methodological reasons is necessary for a sham surgery trial to be considered ethically adequate. In the case of gene transfer trial for LINCL, it is not clear that methodological considerations require a sham surgery control group. This is so for several reasons.

First, although placebo controls may be justified to prove efficacy of a new treatment in diseases with high placebo response rates, there is no evidence that such a placebo effect exists in the case of LINCL and thus performing a sham surgery on the children may not be methodologically useful on those grounds.

Second, given that LINCL is a rare disease—indeed, it has orphan disease status—a placebo-controlled study obliges researchers to divide the small number of children affected into the experimental and the placebo group, which can result in underpowered trials because of their small size (Buckley, 2008). A placebo arm also would put more pressure on the limited funds available for these trials, particularly if a “null” gene transfer vector would have to be produced and rigorously tested.

Third, while one might argue that a sham surgery group is necessary to blind researchers so as to minimize bias in assessment of study end points, a randomized sham surgery control group is not the only way to eliminate possible bias. Another feasible option is to videotape the pre- and post-gene transfer examinations for subsequent quantitative, treatment status-blinded assessment by several independent pediatric neurologists. The neurologists could ascertain whether there are any pre- and posttreatment differences. Similarly, independent, blind review of assessment tools such as magnetic resonance imaging (MRI) tests could also provide evidence about possible differences in the brains of the children who underwent gene transfer.

Fourth, it is true that a sham surgery control group could be used to blind parents who might indeed be quite responsive to placebo effects. But this would be methodologically important only if reliance on parents' observations about their children's improvements after the experimental procedure is one of the primary outcome measures. If, however, parental evaluation is used as a secondary outcome parameter only, then blinding of parents is less pressing on methodological grounds.

It seems then that a sham surgery control is not methodologically required to obtain adequate evidence of the efficacy of gene transfer for LINCL. Nonetheless, as mentioned earlier, the ethical legitimacy of placebo trials is grounded not only on scientific considerations but also on ethical ones. Thus, even if the sham surgery was thought to be justified on methodological grounds, ethical requirements constrain what we can do to human subjects for the sake of scientific knowledge. Following the so-called gold standard of scientific evidence in these trials may violate ethical requirements to (1) not expose human subjects to excessive risks for the sake of scientific investigation; and (2) ensure that risks are reasonable in relation to anticipated benefits.

Indeed, arguably ethical and regulatory reasons do not support a control group in these types of trials when children are the subjects of the research. Current federal regulations (45 CFR 46 Subpart D) limit the research with children that Institutional Review Boards (IRBs) can approve to studies that involve: (1) no more than minimal risk; (2) greater than minimal risk, but presenting the prospect of direct benefit to the individual child; and (3) minor increase over minimal risk without the prospect of direct benefit if the research is commensurate with the subjects' previous or expected experiences and likely to produce generalizable knowledge about the subjects' disorder or condition (DHHS, 1991). Although not approvable by IRBs, federal regulations also allow for research with children that involves greater than minimal risk and no prospect of direct benefit when such research presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children (DHHS, 1991).

Assessing risk and potential benefits in these types of trials is quite difficult. While the field of gene transfer has made important progress both towards scientific knowledge and clinical applications (Mueller and Flotte, 2008; Feng and Maguire-Zeiss, 2010; Sadelain *et al.*, 2010; Simonelli *et al.*, 2010), such progress has not been without significant scientific complications (Anonymous, 2010; Deakin *et al.*, 2009; Williams, 2009; Wilson, 2009). Thus, evaluating risks and uncertainty in gene transfer trials remains difficult because of their level of complexity, the lack of a widely accepted system for quantifying the risks, and adverse events encountered in several of the trials conducted being unanticipated (Kimmelman, 2008; Williams, 2009; Wilson, 2009). Certainly, this is a problem for gene transfer trials of LINCL whether they involve sham surgeries or not. Thus, careful monitoring, interim analysis, appropriate stopping rules, and other safety procedures are necessary to ensure that subjects do not run unnecessary risks.

Although there is a significant amount of controversy about how to understand “minimal risk” or a “minor” increase over minimal risk (Miller *et al.*, 2003; Kopelman, 2004; Wendler and Emanuel, 2005; Fisher *et al.*, 2007; Iltis, 2007; Lantos, 2007; Glass and Binik, 2008; Litton, 2008), few would consider administration of a viral vector through six burr holes drilled in a child's skull with general anesthesia minimal risk or a minor increase over minimal risk. In contrast to inert substances given to placebo groups, which are presumed to have no adverse effects, sham surgeries can involve significant risks to subjects, as can the use of viral vectors.

Moreover, whereas one can argue that in the experimental group the risks to the children are balanced by the prospect of direct benefit, there is no reason to believe that the control group would receive any direct benefit from the sham surgery procedure. Exposing subjects to excessive risks simply for the sake of scientific advancement, as would be the case for subjects in the sham surgery group, is ethically unjustifiable (Macklin, 1999; Weijer, 2002; Miller and Brody, 2002). Indeed, such would be a paradigmatic case of using a person merely as means to someone else's ends. Moreover, this would be particularly problematic in a trial that involves children with a fatal neurodegenerative disease because they are incapable of consent or assent, not only because they are children, but also because LINCL is a progressive neurodegenerative disorder that involves regions of the brain

associated with cognition (Williams *et al.*, 1999). Subjects in the sham surgery group would be exposed to the risks of a highly invasive surgery and risks related to general anesthesia. Furthermore, if the sham surgery group were to involve the administration of a null vector, it could in theory elicit an antivector immunity. In addition to theoretical risks of toxicity, antivector immunity could preclude the participants from involvement in future trials using similar vectors or it could make them ineligible to receive future effective therapy if the clinical trials were to be successful. Hence, the more presumably rigorous the placebo control is, the more risks it involves. Similarly, because assessment of outcomes would require performance of multiple MRI scans and because these children need to be anesthetized to have the procedure, this would expose them to additional risks.

Randomization

Randomization is another aspect of RCTs that brings to the forefront possible conflicts between scientific methodology and ethical standards in the case of gene transfer for LINCL. As with placebo-controlled groups, from a purely scientific point of view, randomization is often an appropriate methodological requirement. Presumably, dividing subjects into experimental and control groups by following some random process can control all known and unknown confounding factors and can eliminate potential selection bias. Some have argued, however, that randomization is not necessary to avoid selection bias (Worrall, 2002). The main reason why randomization eliminates selection bias is because the procedure of random allocation prevents the experimenter from determining to what arm particular subjects will be assigned. But if the trial is double blind, then randomization plays no further role in this respect.

Furthermore, even in trials in which researchers are not blinded, other means of preventing researchers from determining a division into experimental and control groups would be equally effective in eliminating this potential bias (Worrall, 2002). Moreover, even if selection bias does play a role, in most cases this is unlikely to make a major difference to the outcome of a trial (Worrall, 2002, 2010). Similarly some have argued that randomization, as it is practiced in clinical trials, cannot control for all known and unknown confounders (Urbach, 1985; Howson and Urbach, 1993; Worrall, 2002). Clearly, it is not the case that randomization is a sufficient condition for establishing that any observed effect is necessarily the result of the experimental treatment under consideration. In any particular randomized division, it is entirely possible that some factor known or unknown is unbalanced between the experimental and the control groups.

But, as was the case with placebos, whether randomization is presumed to affect the scientific validity of a trial or not, ethical considerations need to be taken into account when deciding whether it should be used in a gene transfer trial for LINCL. Indeed, randomization in these types of trials presents several practical problems with ethical implications. Some evidence suggests that people in general are less likely to participate in clinical trials if they involve random allocation to study arms or placebo controls (Robinson *et al.*, 2005; Agoritsas *et al.*, 2011). Moreover, as indicated earlier, LINCL is not only a rare disease but a fatal one in childhood. It should come as no surprise then that if parents are presented with the option of

enrolling their children in a trial that requires randomization to a control group they will be quite reluctant to enroll their children in such a trial. Whether rightly or wrongly, parents will tend to believe that the experimental procedure being tested is the best option for the fatal disease their children have. They might thus feel compelled to pursue other options, such as poorly documented, stem cell interventions offered in China (Qiu, 2009; Caplan and Levine, 2010; Zarzeczny and Caulfield, 2010). If the control group involves not only a placebo, but one that involves a risky surgical intervention, then it is even less likely that parents will be willing to expose their children to the risks of the study.

Conducting RCTs of gene transfer for LINCL also involves other practical constraints with ethical implications that arguably make the RCT gold standard less golden. A significant concern is related to financial feasibility. An RCT would be significantly more expensive than other options. While the financial incentives of the Orphan Drug Act of 1983 make drug development for these diseases somehow attractive to pharmaceutical and biotechnology companies, the fact that a drug will be required by only a small number of patients still makes orphan diseases unappealing to industry (Anonymous, 2010). Similarly, funding from federal and advocacy group sources for these diseases is scarce and, in the case of advocacy groups, also involves ethical issues that need to be addressed (Arkin *et al.*, 2005). Hence a randomized placebo trial might be financially unfeasible in this case.

Nonetheless, having a control group would arguably strengthen the results of clinical trials testing gene transfer for LINCL. As we have seen, however, such a control need not require a sham surgery arm in order to provide adequate evidence of efficacy. Moreover, it need not require randomization either. The control arm could involve a combination of a contemporaneous control group that undergoes all the same follow-ups at a subset of time points but has no surgical interventions, pretherapy data to use the children as their own controls, and data from past and ongoing natural history studies (Worgall *et al.*, 2008). It is true that a contemporaneous control group might face some problems, such as the fact that parents will want to have their children receive the experimental intervention and that even if enrolled in the control they may have less incentive to comply with study visits. Nonetheless, prior experience (Worgall *et al.*, 2008) suggests that some parents will opt for a non-experimental intervention option and thus this might allow the recruitment of subjects for a contemporaneous control group. Such a group added to data from using the children enrolled in the experimental arm as their own controls and from historical data is likely to generate sufficient data to allow for an efficacy comparison.

Based on these concepts, we have designed a clinical trial for LINCL with a contemporaneous control group (Fig. 1). The trial is similar to the completed AAV2-based trial but uses the nonhuman primate AAVrh.10 vector to deliver the human CLN2 cDNA to the CNS (Worgall *et al.* 2008). Pre-clinical studies in rodents and nonhuman primates have shown that the AAVrh.10 vector is superior to any other AAV serotype in delivering the CLN2 cDNA and its tripeptidyl peptidase product throughout the CNS (Sondhi *et al.* 2007, 2008). For recruitment into the trial, if the preliminary data suggest eligibility, subjects are screened in the order they have contacted us, and then, if eligible, offered the

FIG. 1. Overall design of the AAVrh.10hCLN2 trial of gene therapy for children with late infantile neuronal ceroid lipofuscinosis (LINCL). Subjects with LINCL are evaluated in a “screening protocol” in which the diagnosis is confirmed and the clinical status of the child is assessed by a clinical rating scale and central nervous system magnetic resonance imaging. If one of the two parental CLN2 alleles is one of the five most common genotypes, and the child is mild to moderate on the Weill Cornell LINCL scale (Worgall *et al.*, 2007), and fits all of the other inclusion/exclusion criteria, the child is considered “eligible” by a committee of four faculty, independent of the Principal Investigator (PI). In a consent process independent of the PI, which includes a patient advocate from the Weill Cornell NIH Clinical Translational Science Center, the family is given a choice to continue the screening protocol ($n = 16$; “untreated”) or enter into the gene therapy “treatment” protocol ($n = 16$). The treatment group will be in two dose cohorts, total dose 9×10^{11} genome copies (gc) or 1.8×10^{12} gc. The untreated group will be reassessed for efficacy parameters at 18 months and the treatment group at 6, 12, and 18 months.

opportunity to participate. When subjects are screened and they fit the criteria they are invited to participate and have an opportunity to enter the “untreated” or “treated” arm based on the decision of the parents, guided by a patient advocate not involved in the trial. This trial was designed with input from the U.S. Food and Drug Administration (FDA). Based on this input as shown (Fig. 1) the treatment/vector arm has two dose cohorts; therefore, if the subject decides to participate in this arm he or she will go to the dose cohort ongoing at that time. The lower dose cohort has to be completed first. A detailed report has to be submitted to the FDA at the end of this cohort. If the FDA agrees that there are no safety concerns, the study will proceed to the higher dose cohort. There is no randomization as the two dose cohorts are done sequentially and not in parallel.

Conclusion

Often it is the case that following the highest standards of scientific evidence engenders no conflicts at all with the ethical obligation to protect human subjects. But at times, what scientific research is thought to necessitate is constrained by ethical requirements. It is important, however, to appreciate the complex interrelations between ethics and considerations about scientific evidence (Worrall, 2008). Hence, if one believes that the only adequate evidence about treatment efficacy for LINCL is that acquired from properly performed RCTs, then, one is likely to accept that the performance of other types of trial designs would be unethical,

as these other trials would expose participants to risks with no expectation of generating reliable, generalizable, and interpretable evidence. If, on the other hand, one believes that trial designs other than RCTs will provide a sufficient degree of confidence that the procedure is beneficial, then one might conclude that high risks to the controlled group are unjustified and thus that an RCT will be unethical.

Clearly, considerations about the challenges of designing randomized clinical trials for orphan diseases have had an effect on the approval process of drugs for these types of conditions. Indeed, as some have pointed out, the approval of drugs for rare diseases has depended less on randomized clinical trial studies than that of other drugs for more common diseases (Buckley, 2008; Mitumoto *et al.*, 2009; Griggs *et al.*, 2009; Anonymous, 2010). Researchers and agencies such as the European Medicines Agency have acknowledged the difficulty of conducting randomized clinical trials when dealing with very rare diseases and have defended other types of trial designs, such as using external or historical controls or participants serving as their own control, in order to allow development of needed medicines (Buckley, 2008; Griggs *et al.*, 2009; Anonymous, 2010).

Nonetheless, even when nonrandomized clinical trials are proposed as reasonable alternatives to a randomized clinical trial design for rare diseases, there is still a tendency to think of these alternatives as providing evidence that does not rank as high as that of randomized trials (Buckley, 2008; Griggs *et al.*, 2009). That is, even when appropriate because of ethical and practical constraints imposed by some

diseases, the evidence obtained by nonrandomized clinical trial is thought to be a “second best.” But claiming that randomized clinical trials provide the best evidence of therapeutic efficacy, presupposes both that such trials are practically feasible and ethically sound. If and when they are not, it does not seem reasonable to defend that they offer the best evidence and that in such cases we have to settle for a second best. Indeed, to insist that unfeasible and unethical randomized clinical trials are the gold standard seems to make the best the enemy of the good.

Acknowledgments

We would like to thank N. Mohamed for editorial assistance. These studies were supported, in part, by U01 NS047458, R01 NS061848, and UL1-RR024996.

Author Disclosure Statement

No competing financial interests to disclose.

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Received for publication September 30, 2010;
accepted after revision March 30, 2011.

Published online: March 31, 2011.