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Ethical Issues in Neonatal and Pediatric Clinical Trials

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Synopsis

Children have been identified as uniquely vulnerable clinical research subjects since the early 1970s. In this paper we review the historical underpinnings of this designation, the current regulatory framework for pediatric and neonatal research, and common problems in pediatric research oversight. We also present three areas of pediatric and neonatal research (genomic screening, healthy children donating stem cells, and therapeutic hypothermia for neonates with hypoxic-ischemic encephalopathy) that highlight contemporary challenges in pediatric research ethics, including balancing risk and benefit, informed consent and assent, and clinical equipoise.

Keywords

Ethics; research; informed consent; Risk-benefit assessment; Clinical trials; Stem cell transplantation; Genetic testing; Hypoxic ischemic encephalopathy

The Dawn of Pediatric Research Ethics

The unique vulnerability of children as research subjects came to light when Henry Beecher published a landmark article in the *New England Journal of Medicine* entitled, "Ethics and Clinical Research."¹ Beecher's paper catalogued a number of research studies that he argued were ethically unacceptable. One of them was a study by Saul Krugman and colleagues, conducted at the Willowbrook State School, a residential facility for children with neurocognitive problems. In Krugman's studies, some children were deliberately infected with hepatitis in order to study the natural history of hepatitis and better characterize

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different types of hepatitis – with the ultimate goal of developing a vaccine against hepatitis. Although these studies were done with parental permission, Beecher argued that they were unacceptable because the risks to the children were too high and the informed consent process lacking: “Artificial induction of hepatitis was carried out in an institution for mentally defective children in which a mild form of hepatitis was endemic. The parents gave consent for the intramuscular injection or oral administration of the virus, but nothing is said regarding what was told them concerning the appreciable hazards involved” (p. 1359)

Other critiques of Krugman’s studies soon followed. In 1970, theologian Paul Ramsey wrote of the Willowbrook studies: “Such use of captive populations of children for purely experimental purposes ought to be made legally impossible ... stopped by legal acknowledgement of the moral invalidity of parental or legal proxy consent for the child to procedures having no relation to a child’s own diagnosis or treatment.”² Five years later, the *Lancet* published an exchange of letters about the Willowbrook studies. Steven Goldby wrote that “it was indefensible to give potentially dangerous infected material to children, particularly those who were mentally retarded, with or without parental consent, when no benefit to the child could conceivably result.”³ Krugman (1971) himself wrote back, defending the studies on the grounds that the children involved did, in fact, benefit, because

“(1) they were bound to be exposed to the same strains under the natural conditions existing in the institution; and (2) they would be admitted to a special, well-equipped, and well-staffed unit where they would be isolated from exposure to other infectious diseases which were prevalent in the institution—namely shigellosis, parasitic infections, and respiratory infections—thus, their exposure in the hepatitis unit would be associated with less risk than the type of institutional exposure where multiple infections could occur.”⁴

This debate polarized the research community. The editors of the *Lancet* criticized the Willowbrook studies⁵ and suggested that they would no longer publish Krugman’s papers. In contrast, the editors of the *Journal of the American Medical Association* published Krugman’s follow-up studies, along with a laudatory editorial criticizing the “pious tone” of the *Lancet* editorial and suggesting that Krugman’s studies were ethically justifiable⁶. A decade later, medical historian David Rothman (1982) wrote of Willowbrook that the parental consent was meaningless because “[t]he consent form that parents signed to allow their children to be infected with the virus read as though their children were to receive a vaccine against the virus.”⁷ Furthermore, he argued, parents often consented to the studies in order to get their children out of the overcrowded wards at Willowbrook and into the far superior accommodations of the research wing. Thus, he argued, the “benefit” of better care in the research wing of Willowbrook was, in fact, a coercive inducement to participate in the studies. Such a justification for research, he suggested, would specifically put poor children at risk of participating in the most risky research.

The debate over Krugman’s Willowbrook studies illustrates a central feature of the ongoing debates about pediatric research, specifically which studies are justifiable, for which populations of patients, and with what safeguards and oversight. Many children cannot participate in decisions about their participation in research. Even those who can participate in such decisions may not be able to fully understand the risks and benefits. Parents, physicians, and scientists all have an obligation to protect children from the harms of research but they may also fervently hope to discover new treatments or cures for childhood illnesses. The tension between these two goals – protection and progress – is inevitable.

Reasonable people can disagree about the proper balance in any particular intervention. Those disagreements occasionally rise to the level of public scrutiny. Specific controversial studies become paradigm cases that serve as the basic building blocks of the unique body of

moral philosophy that is the foundation of pediatric research ethics. In this paper, we will review both the current federal guidelines for research in children as well as some interesting controversies that illustrate – and test – the application of those guidelines.

Tags: Research ethics, Willowbrook study, Vulnerable subjects

Ethics and regulatory oversight of pediatric research

Research that involves children has always been ethically problematic. The fundamental reason is straightforward. Research, by its very nature, uses subjects as a means to the end of creating generalizable knowledge. In adults, the solution to this fundamental ethical problem is to get the voluntary, informed consent of the research subject. Children cannot consent on their own behalf. Instead, researchers, parents, and regulators must determine whether the risk-benefit ratio is acceptable in order to permit the research to go forward.

The regulations governing research conduct in the United States have always included special requirements and considerations for pediatric research subjects and other vulnerable populations. These special requirements call for a higher level of scrutiny and more stringent thresholds of protection than for less vulnerable populations.

While the reasons for extra scrutiny of pediatric research are straightforward, the arguments for the necessity of doing research in children are also compelling. Children, and particularly infants, respond differently to drugs and other medical treatments than do adults. There are many stories of drugs that, while safe in adults, have serious and even fatal side effects in children⁸. Studies in children often require longer follow-up than do studies in adults in order to determine whether innovative treatments have any long-term developmental effects.

The current regulatory guidelines for pediatric research define four levels of riskiness in research studies, each of which is subject to a different level of regulation and oversight (table 1). The lowest level of risk is “minimal risk.” Minimal risk is defined as ‘the probability and magnitude of physical or psychological harm that is normally encountered in the daily lives, or in the routine medical or psychological examination, or health children’ (National Commission – *Research Involving Children*^{9,10}). Studies that involve only minimal risk can be carried out, even if they do not offer any prospect of direct benefit to the research subjects. For such studies, researchers only need the permission of one parent and the assent of the child – if the child is old enough and cognitively capable of giving assent.

Unfortunately, this categorization is problematic because it is vague. First, the definition does not specify whether these risks should be interpreted relative to normal, healthy children, or relative to the sick children who are like those to be enrolled in the study. The “normal daily lives” of *sick* children might include invasive procedures, treatments, and discomforts. Second, the daily life of a child can be quite risky. Children are at risk of injury when they ride a bike, play competitive sports, take ballet lessons, or climb trees, but these risks seem different from those to which a child is exposed in a research study.

This vagueness creates variable interpretations by investigators and institutional review boards (IRBs).¹¹ In a survey study of IRB chairmen, Shah and colleagues identified marked variation in assessment of the level of risk associated with different procedures – for example, allergy skin testing was found by 23% of those surveyed to be minimal risk, by 43% to convey a minor increase above minimal risk, and by 27% to impose more than a minor increase over minimal risk; similar variation was observed in assessment of potential for direct benefit.¹²

The second level of risk is called “a minor increase over minimal risk.” Research with this level of risk – and with no prospect of direct benefit to the research subjects, may still be approved by an IRB, but only if the research is likely to yield knowledge that is of vital importance to understand or ameliorate the child’s disorder or condition. The research risks are acceptable if they are commensurate with those in the child’s actual or expected medical, dental, psychological, social, or educational situations. For research in this category, the permission of both parents is required, as is the child’s assent (again, if the child is developmentally capable of providing it).

The third risk category is for studies that involve risks that are greater than minimal or even minor increase over minimal risk but that also include the prospect of direct benefit to the child. These studies were previously referred to as “therapeutic research” but that term has gone out of favor. In such studies, the task of the IRB is to conduct a risk-benefit assessment and to determine whether the potential anticipated benefit justifies the risk. While tangible, quantifiable information about the likelihood of these risks and benefits may be available, ultimately this assessment may be somewhat subjective.¹³ Conduct of these studies requires the consent of one parent and the assent of the child.

Implicit in the ethical conduct of studies that fall into this third risk category is the assumption of “clinical equipoise.” First described by Benjamin Freedman, “clinical equipoise” is defined as “a state of genuine uncertainty on the part of the clinical investigator regarding the comparative therapeutic merits of each arm in a trial.”¹⁴ However, as Freedman also pointed out, these studies cannot be absent of merit: “Equipoise is an important concept in the conduct of ethically sound pediatric research, which must be conducted in pursuit of findings that are of scientific merit.” According to Freedman, clinical equipoise exists when there is “an honest, professional disagreement among expert clinicians about the preferred treatment.” An ethically sound clinical trial should offer reasonable hope of resolving this disagreement. Conversely, if existing evidence clearly favors one treatment or another, or if the proposed trial is unlikely to disturb the state of equipoise, the trial should not proceed as designed. Research must be done in authentic pursuit of answers to valid clinical questions, and patients should not be subjected to research risks in the absence of genuine belief that the answer to the research question is unknown. This is not different for research that involves children. In the initial interpretation of the National Commission’s recommendations for research involving children, Albert Jonsen described the need for this research to be “valuable and necessary for the health and wellbeing of children.”¹³

The fourth risk category is the most complex and the most unusual. It is for studies that involve more than a minor increase over minimal risk, no prospect of direct benefit for the child, but that are judged to be so important, in terms of the knowledge that they might yield that they ought, perhaps, to be conducted anyway. Studies that meet these criteria must be ones that are likely to yield knowledge that will prevent or alleviate a serious health condition in childhood. IRBs cannot approve these studies. If an IRB determines that a proposed study meets these criteria, they need to refer the study to the federal government, which will convene an expert panel to review the proposed study and to decide whether it may go forward. Such studies, if approved, require the permission of both parents and the assent of the child.

Tags: risk-benefit assessment, informed consent, institutional review board (IRB), research oversight

The complicated concept of “assent”

All research in children requires the assent of the child. But what is assent, exactly? At what age is a child capable of assent? When should it be sought? As with “minimal risk,” answers to all of these questions are vague and variable. At the most basic level, assent is an affirmative agreement by the child to participate in research. William Bartholome, one of the strongest advocates for the necessity of assent, broke it down into four elements. “1) a developmentally appropriate understanding of the nature of the condition, 2) disclosure of the nature of the proposed intervention and what it will involve, 3) an assessment of the child’s understanding of the information provided and the influences that impact on the child’s evaluation of the situation, and 4) a solicitation of the child’s expression of willingness to accept the intervention.”¹⁵ These elements notwithstanding, there is active debate about the definition of assent, its process, and the age when a child can provide it. Roth-Cline and colleagues point out the controversies about assent, “how to resolve disputes between children and their parents; the relationship between assent and consent; the quantity and quality of information to disclose to children and their families; how much and what information children desire and need, the necessity and methods for assessing both children’s understanding of disclosed information and of the assent process itself; and what constitutes an effective, practical, and realistically applicable decision-making model.”¹⁶ Unguru and colleagues interviewed children aged 7 to 19 about their experience in oncology trials and discovered that many children did not understand basic aspects of the research (for example that there might be added risk compared to standard treatments), and did not actually feel that they were able to play a significant role in decision making.¹⁷

In the absence of validated processes for engaging children in meaningful, developmentally appropriate exchange of information about research participation, the process of obtaining assent before enrolling children in research studies is at risk for the same pitfalls that plague the informed consent process for adult research subjects, including cumbersome and legalistic documents and minimal critical evaluation of comprehension. Furthermore, for studies in which the anticipated benefit is thought to outweigh the risk – such as clinical trials of cancer chemotherapy, the parents may claim the right to override the child’s dissent. In such studies, it is not clear whether the guiding moral framework should be the research paradigm or the ethical paradigms that govern non-research clinical care in which parents have the right to make decisions for their children.

Not surprisingly, IRB chairs are as variable in their interpretations of assent as they are in their interpretations of minimal risk. Whittle et al. found that half of IRB chairs rely on the investigators’ judgment about when assent must be sought; the other half had a required method for investigators to determine whether obtaining assent was appropriate, most commonly based on age, but the age cutoff for requiring investigators to obtain assent from the child ranged from ages less than or equal to 5 years, and older than or equal to 10 years.¹⁸

Tags: assent

Problems with the current regulatory framework

Despite the recognition of the importance of research oversight in protecting children in research studies, the existence of the federal regulations for child research participants have not brought harmony or efficiency to the process of bringing pediatric research protocols to fruition. The process of research oversight by IRBs remains cumbersome for reasons that are both logistic and ideological. The following problems are commonly identified as most obstructive to ongoing research in pediatric populations:

1. Disconnect between the level of required scrutiny and the level of risk, such that minimal risk studies are still subjected to long and onerous review processes.
2. Inter-institutional variation in interpretation of research protocols and regulations which requires multi-center trials to submit different protocols at the participating centers resulting in not only delayed but sometimes also weakened investigations
3. Vagueness in the regulations about the likelihood of benefit, burden of interventions, and acceptability which leads to disagreements within an IRB that result in a prolonged review process.
4. Volunteer system of IRB reviewers, who may have limited background knowledge of the research subject area, incomplete understanding of the regulations, and limited time and resources to devote to methodological and thoughtful consideration of a proposed protocol.
5. Cumbersome and lengthy informed consent documents, weighed down by boilerplate language included to protect institutions rather than inform and protect children and their parents. The emphasis on an institutionally uniform and comprehensive informed consent document, which may detract from a more relevant and meaningful interactive process of discussing a study's potential risks and benefits with children and their parents.

These problems no doubt lead to investigator cynicism and development of protocols that “teach to the test,” such that there is disconnect between the process of research oversight and a more meaningful one actually protecting child research subjects. Protocol approval is not a guarantee that a study is ethical, and an ethically designed study is not guaranteed to be approved.

Tags: informed consent document, IRB

Proposed Changes to Regulations

In July of 2011, the Office of the Secretary of the Department of Health and Human Services issued advance notice of proposed rulemaking (ANPRM), seeking comments on suggested changes to existing human subject protection regulations in order to make these rules more modern and effective (table 2). These proposed changes were designed to include contemporary problems in research ethics, such as use of bio-specimens and electronic medical records, need for systematic approaches across institutions regarding informed consent and scientific review, and categorization of exempt and minimal risk research. An exhaustive review of the proposed changes is beyond the scope of this paper, but we will briefly describe some of the proposed changes with the potential to directly impact pediatric research. These include:

1. No current system for standardized data security protections – addressing this has the potential to ameliorate what many view to be excessively burdensome oversight of minimal risk studies, many of which are limited to chart review or evaluation of previously collected data or samples.
2. No consent required for use of de-identified existing bio-specimens, which may ultimately be able to re-linked to individual identifiers.
3. Common rule only enforceable if research is funded by certain sources, introducing inconsistency in the way research is conducted in the U.S. with regard to ethical principles, which ought to be universal.

4. No systematized way to report adverse events, minimizing the likelihood that important safety information will be consistently reported to regulatory bodies and investigators.
5. Burdensome yet inadequate requirements for informed consent, with¹⁹ inordinate amounts of attention and effort dedicated to the informed consent document, rather than focusing on presenting information to potential research subjects in an informative way required by IRBs and investigators
6. Multiple IRBs to review the same protocol for multicenter studies – this can be cumbersome for local IRBs, which may not have reviewers with the highly specialized expertise needed to evaluate some complex clinical trials²⁰, and delay or even thwart efforts to carry out timely multicenter clinical studies¹⁹. A streamlined process of centralized regulation and oversight has the potential to both improve the quality of research oversight and to support investigators conducting important multi-center trials.

Tags: proposed changes to research oversight, common rule

Controversial research in children

There are many examples of the difficulties in following the current regulations for pediatric research. We briefly discuss three – studies of genetic screening, the enrollment of healthy children in studies of sibling bone marrow donation, and the use of hypothermia for neonates with asphyxia.

Genetic Testing Research in Children

Genetic testing research in children presents pressing ethical challenges in pediatric research. While “genetic testing research” encompasses vastly different types of research that require distinction prior to any discussion about risks and benefits,²¹ herein we focus on research that identifies active or future disease risk to the individual being tested. Although the ethical issues that surround testing for carrier status – when individuals carry a genetic change that does not cause for themselves but can be passed on to offspring – are important, they are beyond the scope of this paper.

The first distinction of genetic testing research in children is whether the research involves genetic testing of symptomatic or asymptomatic (i.e., healthy) children. For example, genetic testing studies may involve children with clinical findings (e.g., congenital anomalies, developmental delay) that lack an underlying genetic diagnosis. Some of these studies recruit and study families with multiple members who have a similar constellation of symptoms and/or physical findings for which an underlying genetic etiology is sought.²² Others involve large cohorts of unrelated patients with diverse and complex phenotypes whose entire genomes are examined to identify genetic alterations that might explain the observed phenotype.²³

For affected children and families who participate in these types of genetic testing research, the benefits of this kind of research – etiologic diagnosis that may inform future treatments and reproductive decisions – are deemed to outweigh the risks. There are greater concerns about the psychological harms of receiving the research results than on undergoing the research process (e.g., consent for use of samples, privacy of results). For example, there are potential threats to individual and familial identity caused by the identification of a genetic condition (e.g., parental/familial guilt),^{24,25} revealing information about other family members who might carry the same predisposition. Uncertainty about the causality of the research findings may be quite important. Parents might expect (and hope) for definitive

answers about their child's illness. They may use the research findings in making future decisions about their child's health and their own future family planning. As a result, there has been a call for careful attention to the process of returning research results to these children and their families.²⁵

Most genetic testing research among *asymptomatic* children has focused on Mendelian disorders (i.e., those caused by mutations in single genes and that are minimally influenced by environment) such as Huntington disease or Li-Fraumeni syndrome. In the coming decade, pediatric genetic testing research will grapple with ethical challenges that result from the ability to sequence an individual's entire genome. This technology will allow research on genetic susceptibility testing (also referred to as "predictive genomic testing") and lead to challenges related to incidental findings as vast quantities of information, some unanticipated, are generated. The term "genomic" reflects the fact that this testing assesses disease risk for common complex diseases, such as type 2 diabetes. The term "complex" refers to the influence of both genetic (usually across multiple genes) and environmental factors on disease development. Unlike in Mendelian diseases, where the risk of disease is almost always 100%, genetic susceptibility testing provides disease risks that are modestly increased above that of the population, in the order of 10%.

In either type of genetic testing research of children – Mendelian or common diseases – risk/benefit considerations are influenced by 1) the timing of disease onset (i.e., childhood or adult) and 2) treatability of disease. Predicting an early-onset disease (i.e., one that manifests during childhood) carries with it more potential urgency and relevance to the child's life than one that occurs during adulthood. This urgency is only increased when the disease can be cured or its complications can be mitigated. For example, while there is no disease cure for Li-Fraumeni syndrome, the child may benefit from regular cancer screening since the disease can carry a nearly 20% risk of childhood malignancy²⁶. As the treatability of the disease decreases, the benefits of testing shift more to the psychosocial realm, such as helping to prepare for future health and life decisions (e.g., long-term care insurance, child-bearing). Any potential benefits from genetic testing research in childhood are significantly tempered when the child will not develop disease until adulthood. A commonly cited case is identification of children with Huntington disease. There is debate whether a child or adolescent's knowledge of his or her own predisposition to develop adult-onset disease status merits testing during childhood, rather than waiting until the child becomes a competent adult who can provide autonomous consent to participate in this kind of research.²⁷ In fact, many professional societies recommend deferring such testing,²⁸ as many have argued that imposing this knowledge, interferes with the child's "right to an open future"^{29,30}, a term that captures a child's right to preserve their future life options by limiting the decisions and information imposed upon them by others.

Genetic susceptibility testing in children is an emerging field likely to generate significant debate and controversy in the pediatric ethics community. There has been strong opposition to this type of genetic testing research, because of concerns that it will cause significant psychological harm, specifically a fatalistic approach to one's health. The implications are that genetic risk is somehow exceptional and that it differs in some fundamental ways from other clinical risk factors for disease such as blood pressure or obesity. Proponents of conducting research on – not providing clinical services for – genetic susceptibility testing, point out that studies thus far have failed to support this concern³¹ and that this testing involves diseases that are frequently adult-onset, but early preventive behaviors may improve long-term health outcomes³². Here there is clearly tension between protection and progress: on the individual level, research in this area should not subject children to unnecessary risk. However, not conducting the research may lead to inadvertent harm on a

societal level, as the technology is likely to find its way into the clinical realm, whether or not it has been subjected to rigorous scientific evaluation.

Research on healthy children who donate stem cells to siblings

As allogeneic hematopoietic stem cell transplantation has become standard treatment for a number of oncologic and hematologic illnesses that affect children, HLA-matched biological siblings, who are also children, may be identified as potential stem cell donors for these pediatric patients.³³ The American Academy of Pediatrics has supported this process, which is now performed without much controversy in clinical practice. Yet evaluating risks and benefits to a child of donating bone marrow to a sibling is difficult. How does one quantify the potential benefit of saving the life of a child by donating bone marrow to a sibling with cancer? Can this be considered to be direct benefit to the child? What kinds of risks to the donor are reasonable? In addition, scientific questions continue to emerge and evolve, bringing forth questions about the ethics of enrolling child stem cell donors in clinical research. When siblings are to donate stem cells in a research context, the IRB must apply the guidelines above to categorize the risks and benefits. In this scenario, careful interpretation and application of existing regulations for research involving children becomes critical. If there is perceived direct benefit, then research that imposes more than minor increase above minimal risk may be justified. Otherwise, the research should impart no more than minimal risk.

What should be the point of comparison for these donor children? Does it make sense to compare the potential burdens to a sibling donating bone marrow to those accrued by healthy children in day to day life? Surely, ordinary life takes on a different meaning for a child who has a sibling with a serious cancer.

A recent protocol made the questions even more complex. Investigators proposed to give the donors granulocyte macrophage colony-stimulating factor (GM-CSF), a treatment generally thought to be safe but one with potential long-term risks, in order to improve the likelihood of success for the recipient.³⁴ This proposed research deemed to entail more than a minor increase over minimal risk with no prospect of direct benefit to the donor, and in 2008 the FDA Pediatric Advisory Committee's Pediatric Ethics Subcommittee reviewed this protocol and considered whether a third party should advocate for the donor, whether parental discretion can credibly be based on assessment of risk and benefit to the donor, and what implications the committee findings would have on future research on healthy sibling stem cell donation. The results of these deliberations are available online.³⁵ Briefly, they concluded that

1. The potential research represented more than minor increase over minimal risk, excluding it from approval as "minimal risk" research that would not require direct benefit
2. That there *were* potential benefits, but these were *indirect*, excluding the research from approval as research with more than minimal risk but with potential direct benefit to the child
3. That potential donors did not have a condition with respect to the protocol, excluding the possibility of approval as research that posed more than minimal risk but with the potential to ameliorate the participant's condition
4. That the protocol offered an opportunity to address a serious problem affecting the health of children, such that in an invocation of the rare, 4th category described above, potential donors would be allowed to participate provided that they had no identifiable risk factors for complications from GM-CSF administration, that an independent third party was available as an advocate for the potential donor, that

the life-threatening nature of some of the potential risks (acute respiratory distress syndrome and leukemia) was disclosed in the informed consent document, and that “all things being equal, preference should go to an older sibling donor.”

Therapeutic hypothermia for perinatal hypoxic ischemic encephalopathy

Research on therapeutic hypothermia illustrates many of the ethical issues in pediatric research. The earliest clinical trials of hypothermia for babies with neonatal hypoxic ischemic encephalopathy (HIE) were conducted in the late 1990s. The first study, done by Gunn and colleagues in New Zealand,³⁶ was designed only to address safety and practicality. There was no anticipation of direct benefit for the babies. The study was approved by a regional ethics committee and parental consent was obtained.

A few years later, Shankaran and colleagues proposed that it would be ethically acceptable to enroll babies in a prospective randomized trial.³⁷ While the criteria for approval aren't included in published reports, we assume that the studies were assessed as having more than a minor increase over minimal risk, but with a prospect of direct benefit.

Over the next few years, many such randomized trials were conducted. A meta-analysis by the Cochrane Library in 2007 reported that, in eight randomized controlled trials, involving 638 term infants, “Therapeutic hypothermia resulted in a statistically significant and clinically important reduction in the combined outcome of mortality or major neurodevelopmental disability to 18 months of age [typical RR 0.76 (95% CI 0.65, 0.89), typical RD -0.15 (95% CI -0.24, -0.07), NNT 7 (95% CI 4, 14)]. Cooling also resulted in statistically significant reductions in mortality [typical RR 0.74 (95% CI 0.58, 0.94), typical RD -0.09 (95% CI -0.16, -0.02), NNT 11 (95% CI 6, 50)] and neurodevelopmental disability in survivors [typical RR 0.68 (95% CI 0.51, 0.92), typical RD -0.13 (95% CI -0.23, -0.03), NNT 8 (95% CI 4, 33)]. Some adverse effects of hypothermia included an increase in the need for inotrope support of borderline significance and a significant increase in thrombocytopenia.”³⁸

At that point, the debate shifted. It was no longer a question of whether enough was known about the innovative therapy – hypothermia – to allow patients to be randomized. Instead, the debate shifted to one about whether the data were so compelling that it would no longer be acceptable to not treat babies with hypothermia.

The debate polarized the research community in neonatology. In 2005, the American Academy of Pediatrics Committee on the Fetus and Newborn noted, “Therapeutic hypothermia is a promising therapy that should be considered investigational until the short-term safety and efficacy have been confirmed in the additional human trials underway. Long-term safety and efficacy remain to be defined.”³⁹ That same year, Papile wrote of hypothermia, “This treatment is best considered an experimental technique for which informed parental consent should be obtained. Widespread application of brain cooling in the care of neonates with hypoxic-ischemic encephalopathy would be premature.”⁴⁰ A few years later, Schulzke and colleagues echoed these cautious sentiments, “Further research is necessary to minimize the uncertainty regarding efficacy and safety of any specific technique of cooling for any specific population.”⁴¹ Kirpalani and colleagues demanded, “...strong evidence of robust, consistent effects in highly valid studies that have enrolled adequate numbers of patients before mandating a new therapy for management of all relevant patients.”⁴²

Others, however, took a different view. Wilkinson and associates, writing in 2007, noted, “We believe that the strength of the existing evidence warrants careful consideration of whether the risks to participants involved in continuing trials are justified.”⁴³ The next year,

Gunn and colleagues noted that, “robust evidence for benefit from current meta-analyses, the remarkable safety profile, the strong foundation in basic science, and supporting evidence from related disease states such as encephalopathy after cardiac arrest...” all dictate that practicing physicians, in consultation with patients and families, should use hypothermia as a treatment for neonatal encephalopathy.⁴⁴

The debate about hypothermia illustrates the difficulty in deciding about two thresholds in the evaluation of an innovative therapy. The first is the threshold of deciding when we know enough about a new therapy to consider clinical trials in neonatal populations. That is, when do we think there is enough evidence of both safety and efficacy so that we are willing to randomize babies to standard or innovative therapy? The second threshold occurs as evidence from such trials accumulates. When do we know enough to say, with confidence, that the innovative therapy is better, worse, or equivalent to the standard therapy? For both thresholds, reasonable people – and reasonable IRBs – can disagree.

Establishing the second threshold has been relatively easy to do for the patients who most resemble those studied in the therapeutic hypothermia trials. Initiating “standard” cooling therapy (3 days of cooling to a core temperature 33.5 degrees Celsius for 72 hours) for term (at least 36 week) infants with moderate or severe perinatal HIE within hours of birth has become standard of care in NICUs in developed countries^{45–47}; this therapy, which was once only available in academic referral centers has been adopted by growing numbers of community NICUs around the country. At least in theory, this practice is quite homogenous, guided by highly specific published protocols and step-by-step instructions on how to offer safe and effective therapy.^{48,49}

The dissemination of this knowledge has made cooling widely available to affected infants and obviates the need for transfer to referral centers or enrollment in complicated research protocols, but only for those patients who meet the rather strict inclusion criteria. However, questions still remain about whether there is opportunity to further optimize the protocols to yield even greater reductions in the incidence of adverse outcomes (which remains high, even among infants who receive standard cooling therapy). What if, for example, cooling infants for a longer than 3 days, or targeting an even lower core body temperature could impart even more benefit without imposing more adverse effects? Questions also remain about whether this treatment could help a more diverse group of babies, such as those who are not recognized to have HIE until after the 6-hour window has passed, or those infants who are born prematurely. Another set of questions remains about whether therapeutic hypothermia is truly beneficial to infants who have the most severe HIE, and whether, for some infants, offering this treatment could redistribute poor outcomes from death to survival with significant neurologic impairment, an outcome that is viewed by some physicians and parents as a fate worse than death.⁵⁰ While subgroup analyses of the larger clinical trials has not shown this to be the case, this method of analysis may not yield results that are as robust as a clinical trial designed *a priori* to evaluate the outcome in question⁵¹; however, at this point it is difficult to imagine that it would be ethically permissible to randomize infants with severe HIE to cooling or placebo.

Some of the residual questions about therapeutic hypothermia are being addressed by ongoing clinical trials – specifically, clinical trials are underway assessing the effect of cooling initiated up to 24 hours after birth, comparing the safety and efficacy of standard cooling to longer and/or deeper cooling, and evaluating cooling protocols for late preterm infants. Work is also underway to address strategies to initiate therapeutic hypothermia at smaller community hospitals and to continue it during transport to referral centers, as well as to evaluate the value of any number of adjuvant clinical therapies, all with the hope of reducing the incidence of death and disability for babies with HIE.

All of this research is resource intense, requires careful assessment of risk and benefit, and involves a laborious and often nuanced process of informed consent. At our center we encounter the difficulties of trying to maintain an informed consent process that upholds the *spirit* of the principles of research ethics under significant time pressure (studies of longer, deeper cooling, for example, require randomization before six hours of life) with major logistic obstacles, such as having these discussions over the phone with women at referring hospitals who are immediately post-partum, grappling with the sudden and unexpected illness of a newborn baby. Fully informing families with whom the investigator has no previous relationship of the potential risks and benefits associated with subtly different cooling protocols can be difficult in these circumstances. In placebo trials, such as the late cooling protocols, the concepts of equipoise and randomization must also be described in lay terms, as parents may struggle to understand why it isn't better to offer any therapy with the potential to help their baby.

Equipoise regarding the ongoing research questions about therapeutic hypothermia may also prove to be a major issue that impacts the success of future trials, as neonatologists grapple with generalizability of the initial cooling studies. Does it really make sense for a physician to refer a 7 hour old neonate to a different hospital for cooling trial, when "standard" clinical cooling could just be initiated at the birth hospital, obviating the need for a potentially risky transport and separation of mother and baby? If cooling is safe and effective for infants born at or after 36 completed gestational weeks, is it so unreasonable to offer it to a well-grown 35 week infant with HIE? What is the neonatologist's responsibility to refrain from offering "off-label" cooling, and if these therapies are increasingly available "off-label," why wouldn't a parent of an infant with HIE choose that over a randomized trial?

Tags: genomic screening, genetic testing, genetic research, healthy pediatric stem cell donors, GM-CSF research in children, therapeutic hypothermia for hypoxic-ischemic encephalopathy

Conclusion

We have reviewed three areas of controversy in pediatric research areas - research on genetic screening tests, research involving healthy children who donate stem cells to siblings, and research on therapeutic hypothermia for hypoxic-ischemic encephalopathy. In each area, the challenge for researchers and policy makers is to use the framework of minimal risk, acceptable risk/benefit ratio, parental permission, and child assent to determine which study designs are morally acceptable. In each case, the application of basic principles to the practicalities of the research projects requires careful attention to the details of the study, flexibility in the application of the principles, and opens deliberation about the best way to conduct important research safely in a vulnerable patient population.

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Table 1**Pediatric Research Risk Stratification**

Classification	Definition	Stipulations	Informed Consent
No greater than minimal risk *	- No requirement for benefit to subject	- None	Adequate provisions made for soliciting assent of children and permission of one parent
Greater than minimal risk * - presents the prospect of direct benefit to the individual subjects	- Intervention or procedure presents more than minimal risk AND prospect of direct benefit for the individual subject OR - Monitoring procedure is likely to contribute to the subject's well-being	- Risk justified by the anticipated benefit to subjects - Relation of the anticipated benefit to the risk at least as favorable to the subjects as that presented by available alternative approaches	Adequate provisions made for soliciting assent of children and permission of one parent - Child's assent can be overridden
Greater than minimal risk * with no prospect of direct benefit to individual subjects - Likely to yield generalizable knowledge about the subject's disorder or condition (of vital importance for the understanding or amelioration of the disorder or condition)	- Intervention or procedure does not hold out the prospect of direct benefit for the individual subject OR - Monitoring procedure not likely to contribute to the well-being of the subject	- Risk represents a minor increase over minimal risk - Presents experiences reasonably commensurate with those inherent in actual or expected medical, dental, psychological, social, or educational situations	Adequate provisions made for soliciting assent of children and permission of both parents
Greater than minor increase above minimal risk * with no prospect of direct benefit to subjects	Presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children	Health and Human Services (HHS) may approve after consultation with a panel of experts in pertinent disciplines and following opportunity for public review and comment	

* Minimal risk: the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

Based on Title Code of Federal Regulations Title 45 Public Welfare Department of Health and Human Services Part 46 Protection of Human Subjects Revised June 23, 2005, accessed 5/8/2012; Ross LF. *Children in medical research: access versus protection*. Oxford : New York: Clarendon Press ; Oxford University Press; 2006.

Table 2**Overview of Proposed Changes to Federal Regulatory Framework for Human Subjects Protection**

Ensuring risk-based protections	<ul style="list-style-type: none"> - Refinement of existing risk-based regulatory framework - Calibration of the levels of review to the level of risk - New mechanism for protecting subjects from informational risks
Streamlining IRB review of multi-site studies	<ul style="list-style-type: none"> - Utilization of single IRB review for domestic sites of multi-center studies
Improved informed consent	<ul style="list-style-type: none"> - Improved consent forms - Waiver of informed consent or documentation of informed consent in primary data collection - Strengthened consent protections related to reuse or additional analysis of existing data and biospecimens
Strengthening data protections to minimize information risks	<ul style="list-style-type: none"> - Consistent characterization of information with respect to potential for identification - Standards for data security and information problems
Data collection to enhance system oversight	<ul style="list-style-type: none"> - Establishment of an improved, more systematic approach for the collection and analysis of data on unanticipated problems and adverse events
Extension of Federal regulations	<ul style="list-style-type: none"> - Regulatory protections to all research, regardless of funding source, conducted at U.S. institutions that receive Federal funding from a Common Rule agency for human subjects research
Consistency across Federal regulations	<ul style="list-style-type: none"> - Improvement in the harmonization of regulations and related agency guidance

Adapted from: Human Subjects Research Protections: Enhancing Protections for Research Subjects and Reducing Burden, Delay, and Ambiguity for Investigators; Advance Notice of Proposed Rulemaking. Federal Register. July 26, 2011 2011;76(143):44512–44531