Strategies for More Rapid Translation of Cellular Therapies for Children: A US Perspective

**abstract**

Clinical trials for pediatric diseases face many challenges, including trial design, accrual, ethical considerations for children as research subjects, and the cost of long-term follow-up studies. In September 2011, the Production Assistance for Cellular Therapies Program, funded by the National Heart, Lung, and Blood Institute of the National Institutes of Health, sponsored a workshop, “Cell Therapy for Pediatric Diseases: A Growing Frontier,” with the overarching goal of optimizing the path of discovery in research involving novel cellular therapeutic interventions for debilitating pediatric conditions with few or no available treatment options. Academic and industry investigators in the fields of cellular therapy and regenerative medicine described the obstacles encountered in conducting a clinical trial from concept to conclusion. Patient and parent advocates, bioethicists, biostatisticians, regulatory representatives from the US Food and Drug Administration, and translational scientists actively participated in this workshop, seeking to identify the unmet needs specific to cellular therapies and treatment of pediatric diseases and propose strategies to facilitate the development of novel therapies. In this article we summarize the obstacles and potential corrective strategies identified by workshop participants to maximize the speed of cell therapy translational research for childhood diseases. *Pediatrics* 2013;132:1–8

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**KEY WORDS**  
pediatric clinical trials, stem cell, cell therapy

**ABBREVIATIONS**  
ALD—adrenoleukodystrophy  
BMT—blood and marrow transplantation  
FA—Fanconi anemia  
FDA—Food and Drug Administration  
IRB—institutional review board  
NCL—neuronal ceroid lipofuscinosis  
NHLBI—National Heart, Lung, and Blood Institute  
NIH—National Institutes of Health  
SCD—sickle cell disease  
SMA—spinal muscular atrophy  
TBI—traumatic brain injury

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The successful completion of pediatric clinical trials is hindered by the myriad challenges of conducting research in children. A major obstacle is that the small number of subjects eligible for clinical trial participation may preclude the classic pathway of phase I, II, and III clinical testing. Another obstacle is the inability to rapidly adapt a novel therapy for children, in part because of the child’s inability to give autonomous consent and the lack of adequate research infrastructure for the conduct of clinical trials where multiple sites may be needed for both common and rare childhood diseases or conditions. The Production Assistance for Cellular Therapies Program, funded by the National Heart, Lung, and Blood Institute (NHLBI), convened a workshop to identify the obstacles in cell-based translational pediatric research in the United States and propose solutions based on the experiences of leaders in the field along with patient and parent advocates, bioethicists, biostatisticians, and representatives from the US Food and Drug Administration (FDA; workshop participants). The goal of identifying these obstacles and potential solutions was to initiate changes in the translational pipeline that would enhance the development of meaningful cellular therapies, particularly for children with debilitating or life-threatening diseases.

The purpose of this meeting was not to review every disease for which a cellular therapy existed but rather to illustrate specific obstacles. Many of these obstacles are common to all pediatric translational research, but the focus of this workshop was on the translation of cell-based therapies to pediatric clinical trials. In the 3 sessions, academic and industry translational investigators presented their experiences in the application of cell-based therapies and the lessons learned from their clinical trials. The first session was devoted to the unique challenges of performing clinical research in children with several congenital blood diseases amenable to allogeneic blood and marrow transplantation (BMT) where existing therapy has curative potential but is associated with substantial risks of treatment-related morbidity and mortality. Subsequent sessions focused on the emerging cell-based therapies with curative intent for debilitating pediatric conditions for which only supportive care is available. Each group of presentations concluded with a discussion by a panel of clinician–scientists and industry leaders with expertise relevant to the particular session and statisticians, bioethicists, and representatives of the FDA. The discussions began and ended with a commentary by a patient or parent advocate. The obstacles identified and recommendations for overcoming these obstacles were grouped according to theme and reviewed with workshop participants at the end of the meeting. Without any selection, we report here the consensus that emerged regarding ways to address the barriers to pediatric cell-based translational research.

**OBSTACLES IN DEVELOPMENT OF CELL-BASED THERAPIES FOR CONGENITAL BLOOD DISEASES WITH AVAILABLE TREATMENT**

Allogeneic BMT is the standard treatment approach, with a long track record that has demonstrated curative potential for certain congenital disorders of the hematopoietic compartment. The use of transplantation is limited by the availability of a suitable donor for each affected individual. Novel transplant and nontransplant cell-based approaches are being considered to develop curative therapies for a greater proportion of patients and to reduce the current treatment-related risks while retaining the benefits.

Gene therapy, in the form of transplantation of gene-corrected autologous or allogeneic cell populations, is an alternative therapeutic approach for treating inherited diseases with a monogenic defect, severe combined immunodeficiency, Fanconi anemia (FA), and X-linked adrenoleukodystrophy (ALD). Autotransplantation of stem cells expressing the therapeutic transgene overcomes the lack of a suitable allogeneic donor and eliminates the risks of graft-versus-host disease and prolonged immunodeficiency that are associated with allogeneic BMT. For some diseases, such as infantile complete DiGeorge anomaly, non-BMT options also exist. Currently, unmatched allogeneic thymus transplantation can result in high survival rates (>70%) with recovery of the adaptive immune response.

Workshop investigators outlined the numerous obstacles in the development of clinical trials for SCD, beta-thalassemia, severe combined immunodeficiency, FA, ALD, and complete DiGeorge anomaly, which led to several common themes.

**Identifying Population for Recruitment**

Investigators mentioned the challenge of patient–family recruitment for participation in trials of congenital blood diseases, given that other treatment approaches are available and a high-risk phenotype is not reliably predictable. For example, it is rarely evident which patients with SCD or FA will have severe or rapidly progressive disease or which patients will do poorly with supportive care. Furthermore, it is difficult to recommend a patient for gene therapy when BMT is commonly used for these indications. In addition, clinical end points and biomarkers that help assess benefit are seldom available or even defined.
High Cost

Workshop participants emphasized that the development process for cell-based therapies is slow and costly. Workshop participants mentioned the difficulty of securing adequate funding for incremental research (ie, laboratory and preclinical studies), because National Institutes of Health (NIH) grant mechanisms focus on innovation and impact. In addition, they argued that current NIH grant mechanisms, which have a 5-year life span, are not particularly suitable for slow-accruing, high-cost trials. Such studies may not be attractive to industry because of the cost of prolonged trials with uncertain outcomes and limited market potential because of the rarity of some pediatric diseases.

Lengthy Review Process

Workshop participants expressed frustration with the lengthy review process at local and federal levels, the perceived lack of predictability and variability of requirements, and the burden of monitoring and reporting for trials involving DNA manipulation. Given the restrictive inclusion and exclusion criteria posed by regulatory bodies, multi-institutional trials are crucial to ensure subject accrual, but oversight is costly and time-consuming. Coordination of scientific and ethical reviews for multicenter trials was perceived to decrease the time and cost associated with multiple annual reports for various committees. Uniformly, the investigators called for a more centralized process, asking for a centralized coordinated scientific and institutional review board (IRB) review for multicenter cell therapy trials with some coordination with the Recombinant DNA Advisory Committee and FDA.12,13 Other investigators asked for some consideration of a cooperative review process between US and international regulatory agencies.14 Regulatory pathways are initially constructed with the primary goal of ensuring product safety and the ultimate goal of eventual licensure application for a given biologic or pharmaceutical product. However, the consensus of the workshop participants was that many academic investigator-sponsored investigational new drug applications for cell-based therapies also have a primary goal to assure product and participant safety, yet these investigators are not in a position to pursue a market application (eg, biologics license application). Some workshop participants stated that the standard regulatory licensure approval framework (as opposed to a safety review alone) adds to the burden of the sponsoring academic investigator and the research team. This added burden is perceived to reduce the incentive to take on multiple projects or perform investigator-initiated clinical research.

Limitation of Resources

Cell and tissue manufacturing expertise and shared manufacturing facilities are needed because most medical centers do not have this specialized infrastructure. In addition, appropriate animal disease models to track and evaluate human stem cell populations are needed for optimization of cell-based therapies, particularly those that are gene-corrected. There was general consensus among workshop investigators that the resources necessary to cover costs related to regulatory compliance, data management programs, and long-term follow-up of clinical trial participants were inadequate. Furthermore, reimbursement of clinical research costs is a limiting factor because third-party payers often refuse or delay coverage of the use of novel therapies even with curative intent. Access to investigational cell-based therapies or incorporation of new therapeutic approaches into current practice differs across states.

Trial Design and Analysis

The obstacles identified for the development of future trials for X-linked ALD best illustrate the challenges in trial design for a rare pediatric disease: lack of an animal model to better understand the biology of the disease, lack of genetic or clinical predictive factors that will allow early identification of a severe phenotype before its clinical onset (desirable because early treatment may limit the degree of irreversible damage), lack of sensitive neuropsychological test parameters for comparing responses to therapy with different treatments, lack of a centralized registry to systematically collect long-term data on all patients regardless of therapy, and lack of standardization of clinical or functional and radiographic monitoring parameters to compare results across clinical trials.

OBSTACLES IN DEVELOPMENT OF CELL-BASED THERAPIES FOR CONDITIONS WITH NO CURRENTLY AVAILABLE TREATMENT

For severely debilitating and life-threatening childhood diseases and conditions with no available efficacious treatment, emerging cell-based therapies represent a potential therapeutic option. Although the obstacles may be similar to those of pediatric diseases for which there is an existing but high-risk therapy, the development of new treatments for debilitating and life-threatening conditions is hampered by a general resistance to first-in-human trials in children. There was much debate among workshop participants about the appropriateness of enrolling children in first-in-human clinical trials. As discussed later in this article, several common issues were identified among trials for neuronal ceroid lipofuscinosis (NCL) or Batten disease, traumatic brain injury (TBI), cerebral palsy, spinal muscular atrophy (SMA) type 1, severe
epidermolysis bullosa, spinal cord injury, and a severe congenital heart defect.

**Identifying Population for Recruitment**

There was consensus that recruitment of children to first-in-human clinical trials is challenged by regulatory and ethical considerations. There is an inherent tension between providing only palliative care for a child with a life-threatening illness and including the child in a high-risk, unproven therapeutic trial that is designed primarily to assess toxicity, albeit with some chance of benefit. This tension reflects the concern that children should not be exposed to high-risk interventions where no recognized prospect of direct benefit exists. US regulations on research in human subjects discourage but do not prohibit such interventions in children when the product is in the earliest phases of investigation, and investigators argued that there are pediatric patient populations where such unproven therapies should be considered justifiable, such as in children with life-threatening conditions for which there are no viable treatment alternatives, regardless of whether there is an adult population for which the treatment could be offered.\(^{15}\) To move forward the translation of therapies for life-threatening diseases, consensus is needed on what conditions must be satisfied before children are enrolled in studies of high-risk therapies. Although this symposium was not the appropriate forum to reach a consensus on the ethics of research in children, the clinician–scientists and most workshop participants argued that children are inappropriately excluded from certain research trials. There was agreement that this topic warranted more discussion because children with life-threatening diseases may not qualify for such investigational therapies even when the standard of care is supportive care only.

Another perception was the need to better understand how patient–families decide to participate in clinical trials. Identification of factors influencing decision-making will be important to develop strategies to optimize the environment and manner in which consent is sought, to improve subject and guardian understanding, and to increase enrollment.\(^ {16–18}\) Recruitment of patients with TBI has the added challenge of requiring parents to make rapid decisions, with the resultant impact on the informed consent process due to the urgent nature of the injury. In general, workshop participants concluded that there is a strong need for patient advocacy group involvement in education, clinical trial design, and funding of high-risk innovative therapies for rare diseases.\(^ {19}\)

Another concept proposed was the use of external medical disease experts to avoid conflict of interest by the principal investigator, who is often the treating physician. Such a measure is being used in the recruitment of patients with recessive dystrophic and junctional forms of epidermolysis bullosa. Because severity can be variable and some patients may have disease that is mild enough not to warrant such high-risk therapy, the investigators rely on an expert panel to review all pertinent data for each patient, permitting them to assess disease severity rapidly. In addition, these expert panel members review outcome data as part of their role on the data and safety monitoring board, which in turn allows them to understand the risk–benefit ratio as the trial proceeds. This approach may be particularly valuable in the case of a life-threatening inherited disease when the parents are desperate for some form of treatment. Workshop participants agreed that this approach might also be useful in other high-risk cell-based therapeutic trials for more common pediatric conditions.

**High Cost**

High costs are the result of complex product development and manufacture and are magnified by duplication of efforts at multiple sites, demands of regulatory oversight, and slow patient accrual. Industry sponsorship is perceived as difficult to obtain because of high cost, limited market size, and potential liability. Although IRBs require that researchers identify specific methods to mitigate potential research-induced harm and resolve associated financial and legal liability, there are no mechanisms in place to help researchers address this issue. Workshop participants agreed that the research needed to investigate the use of cell-based products is hampered by the high cost of taking these products through trials, and these costs must be addressed to attract industry interest and investment. The FDA’s Office of Orphan Products Development provides funding for initial phases of development and may help support these types of studies, as described in the next section.

**Implementation Barriers**

Industry-sponsored clinical trials for NCL, SMA type 1, and spinal cord injury illustrated the challenges posed by a lengthy review process. NCL, a neurodegenerative lysosomal storage disorder, is uniformly fatal. Direct central nervous system stem cell transplantation is an attractive alternative for treating lysosomal storage disorders with significant brain disease, primarily because of its potential for cross-correction of neighboring cells lacking a normal lysosomal enzyme. A phase 1 trial of human neural stem cell transplantation into the brains of children with advanced and late infantile NCL focused on the safety and tolerability of multiple invasive procedures. The industry
spons or terminated the next phase (phase 1B) because of cost and accrual difficulties. This NCL clinical trial illustrates the difficulty of implementing first-in-human trials in children, which pose a host of special regulatory and recruitment challenges. Regulators may recommend or require limitation of recruitment to children with moderate to severe disease. Given that developmental milestones generally cease at 1 year of age in infants with NCL, there is a special need for biomarkers or informative clinical outcome measures to assess the benefit of therapy. The existence of multiple investigational products adds another layer of difficulty when trials are competing for very limited numbers of patients. The diagnosis of SMA type 1 is usually made before 3 months of age, and more than 95% of patients die or need full-time respiratory support. To date, no existing treatments can reverse or delay disease progression. An industry-sponsored phase 1 safety study of human embryonic stem cell–derived motor neuron transplantation therapy has been proposed and is under investigational new drug review. This trial requires delivery of stem cells directly into the spinal cord of patients. It has been suggested that this first-in-human trial using an embryonic stem cell derivative cell therapy should be evaluated in adults with a severe neurologic disease, despite recognition that there is no exact duplicate disease in adults. Workshop participants argued that results in adults do not predict what will happen in children. The costs of a complex multi-institutional study addressing cumulative review requirements that delayed trial initiation and changes in corporate interests led to the recent termination of the first phase 1 trial of human embryonic stem cell–derived oligodendrocyte progenitor cells in adult patients with complete thoracic spinal cord injuries. Adolescents and children with spinal cord injury were excluded until the safety and potential efficacy data in adults were available. This trial illustrated that preclinical studies to establish the safety and efficacy profiles of new therapies are costly and time-consuming, and in some cases an appropriate animal model for proof of concept or toxicity evaluation does not exist. Better preclinical animal models closely aligned with human clinical disease are necessary to understand potential mechanisms of action and fates of stem cells. Large preclinical development studies to assess the biodistribution, potential toxicity, and efficacy of the candidate therapeutic cell type can be prohibitively expensive, particularly when they depend primarily on NIH funding.

Workshop participants expressed the need for access to alternative pathways, used under extenuating circumstances, that can be applied to cell-based therapies and will help pave the way for future research and applications. The clinical trial evaluating tissue-engineered vascular grafts for use in congenital heart surgery illustrated certain regulatory pathways, including orphan product designation, available to investigators. The FDA’s Office of Orphan Products Development provides incentives designed to encourage development of drugs, devices, and biologics for use in treating rare diseases. Incentives for drugs and biologics include 7 years of market exclusivity for eligible orphan-designated products, tax credits for clinical studies, waiver of marketing application fee, and eligibility for the Orphan Products Grants Program.

**Limitation of Resources**

Investigators emphasized that research costs for cell-based therapies are extremely high, and it is difficult to obtain adequate funding for clinical trials. There is no clearly identified NIH pediatric cell therapy “home” that advocates for children across all institutes. Research is generally funded in a patchwork fashion, which threatens to derail the research at multiple time points along the research continuum. In addition, there continues to be a need for disease-specific national registries that would permit comparisons either with the natural history of the disease or with other therapies. Several investigators identified and strongly endorsed the need to develop disease-specific national registries to collect clinical and biologic data from patient–subjects treated or managed with supportive care.

Patient advocates voiced frustration with the unreliability and length of time tables to provide clinical solutions for life-threatening and progressively debilitating childhood diseases. The time frame of translational research was seen as too long and delaying the development of potential life-saving therapies. Parents of affected children might be willing to accept certain risks and therefore need to be part of the solution for bringing such trials to implementation. However, they thought their decisions must be based on full disclosure of potential long- and short-term outcomes and access to trial-related information. Their ease of access to industry-sponsored clinical trial information was seen as limited by corporate desire to protect intellectual property.

**Trial Design and Analysis**

The presentations on development of clinical trials for TBI and cerebral palsy illustrated the need for appropriate tools to measure impact of the new treatment. TBI accounts for up to 50% of injury-related deaths in children (0 to 19 years of age), and currently there is no effective treatment. Progenitor cell therapy has shown promise in preclinical and phase 1 clinical trials for management of postinjury cerebral...
edema. The lack of scientific consensus regarding acceptable, clinically meaningful outcome measurement tools beyond mortality for TBI (eg, reliable neurologic measures between investigators across sites) has been an obstacle to trial development and implementation. Similarly, cerebral palsy can be a devastating disease resulting from a number of causes including hypoxic–ischemic encephalopathy and trauma sustained at birth, prenatal infection, abnormal brain development, or in utero stroke.\textsuperscript{21} Transplantation of autologous umbilical cord blood into children with cerebral palsy is being evaluated but without an adequate animal model or biomarkers that can serve as surrogates to assess benefit. Even with a randomized placebo-controlled clinical trial, the lack of reliable tools for measuring benefit is challenging and underscores the need for such tools.

TBI and cerebral palsy clinical trials illustrate the need for preclinical animal models closely aligned with human clinical disease to understand potential mechanisms of action and the role of infused cells and also the need for statistical methods to assess surrogate end points that correlate with long-term outcomes to distinguish between natural history and treatment-related improvement.

**CONCLUSIONS AND SUGGESTIONS TO OVERCOME OBSTACLES IN DEVELOPMENT OF CELL-BASED THERAPIES FOR CHILDREN**

This workshop demonstrated the urgent need for improvement of the overall processes for pediatric translational research, in particular for novel therapies for debilitating and life-threatening childhood diseases. Scientific advances in cellular therapy and regenerative medicine are producing promising therapies for patients with few or no alternative treatments. There is a need for change in the way pediatric translational research is conducted and implemented to optimize the timeline for introducing these therapies into the clinic. A collaborative effort between academia, industry, regulators, and patient advocacy groups will be critical to ensure a more efficient and successful path to therapy development. Workshop participants made the following suggestions to address the aforementioned obstacles identified in the conduct of cell-based therapy clinical trials.

- Investigators and NIH institutes, where appropriate, should establish partnerships with patient advocacy groups to help direct and fund recruitment for future research and to educate the relevant community on the risks and benefits of the novel therapy to engender trust among patient–families and health care providers.
- Investigators and NIH institutes, where appropriate, should facilitate multi-institutional (domestic and international) trial collaborations by trying to harmonize financial and regulatory oversight bodies and centralizing scientific and IRB reviews.
- Investigators and NIH institutes, where appropriate, should work toward establishing external panels of medical disease experts for structuring subject recruitment and assessment of response to cell-based therapies.
- NIH staff should work toward developing funding mechanisms for pediatric cell-based therapies that cut across all NIH institutes and create a virtual home for pediatric cell and gene therapy, ensuring the sharing of strategies for overcoming regulatory, technical, and ethical challenges. For example, the recently established National Center for Advancing Translational Sciences (December 2011) could play a pivotal role.
- The NIH should consider identifying centers of excellence or consortia with established track records that justify long-term (>5-year) investment and release funds for clinical trials by phase and should centralize the development of complex cellular therapies on a larger scale than currently exists with the requisite expertise and regulatory infrastructure.
- Investigators should promote partnerships between academic medical centers and industry and patient advocacy groups to:
  - Establish research models for joint development of clinical trials between academic centers and industry, with adequate protection of proprietary information.
  - Promote incentives for industry to invest in research of rare diseases.
  - Consult patient advocacy groups regarding the design of clinical trials or direct research to ensure optimal enrollment.
- Investigators should work with FDA staff to explore new methods to meet regulatory requirements for different cell-based therapy trials to:
  - Collaborate closely with FDA reviewers to achieve consensus for preclinical study requirements and expectations.
  - Determine safety and clinical efficacy signals needed in early trials.
  - Review and possibly revise the existing mechanisms available to investigators to propose a study with the primary intent to stir additional scientific advancement rather than to provide a direct path to commercial licensure.
- Investigators and NIH Institutes should work to:
  - Establish training and career development for investigators desiring to
pursue cell-based translational research.

Establish appropriate ethical principles for inclusion of children in first-in-human clinical trials.

Advocate for increased support for development of shared manufacturing processes by increasing the visibility of the NHLBI-sponsored Production Assistance for Cellular Therapies program and the Gene Therapy Resource Program.

Develop disease-specific biomarkers for assessing responses to a given treatment and comparing responses between treatments. In addition, biomarkers might provide a strategy for segregating patients between competing trials, ameliorating uneven accrual rates.

Advocate for increased funding for rare disease research by promoting national advocacy for rare diseases and increasing resources of the Office of Rare Diseases Research.

● Investigators should partner with patient advocacy groups to facilitate improved access of patient–families to clinical trial information, as agreed to by the sponsor.

● NIH institutes should work to increase research on innovative statistical methods for analysis of small clinical trials.

● Investigators, industry partners, and patient advocacy groups should advocate for the funding of natural history studies to enable trial design and facilitate comparisons across clinical trials.

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