Review

Pediatric Oncology Research in Low Income Countries: Ethical Concepts and Challenges

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Uneven strides in research and care have led to discrepancies in childhood cancer outcomes between high and low income countries (LICs). Collaborative research may help improve outcomes in LICs by generating knowledge for local scientific communities, augmenting knowledge translation, and fostering context-specific evaluation of treatment protocols. However, the risks of such research have received little attention. This paper investigates the relationship between pediatric oncology research in LICs and four core issues in the ethics literature: standard of care, trial benefits, ethics review, and informed consent. Our aims are to highlight the importance of this field and the need for further inquiry. Pediatr Blood Cancer 2012; 58:492–497.

Key words: ethics review; informed consent; low income countries; pediatric oncology; research ethics; standard of care; trial benefits.

Introduction

Children with cancer in high income countries (HICs) have benefited from substantial advances over the past several decades, and now enjoy average cure rates above 80% [1]. Survival rates in low income countries (LICs), however, are 5–60% [2]. Of the approximately 250,000 children who develop cancer annually, only 50,000 live in HICs [3]. Over the last two decades, pediatric oncologists in both HICs and LICs have begun to address this survival gap through "twinning partnerships," in which HIC and LIC institutions collaborate to improve outcomes for children with cancer [4–7]. Twinning programs have made possible improvements in infrastructure, enhanced access to drugs and diagnostic tests, consultation with HIC experts, and training of local health care providers [8–11].

As such initiatives have improved outcomes in LICs, interest has emerged in conducting research. Pediatric oncology research in LICs has the potential to improve outcomes for LIC children with cancer by generating knowledge for both local and global scientific communities, augmenting resource- and knowledgetransfer activities, and fostering context-specific evaluation of prognostic variables and treatment protocols. However, the concomitant risks of such research have received little attention. The potential for exploitation of patients, families, already overworked clinical staff, and the community as a whole is not insignificant. This risk is greatest when researchers gear LIC trials to answer questions of principal relevance to HICs, with minimal possibility for LIC benefit. Primarily, these risks attach to interventional studies, with drug development trials posing unique risks in the LIC setting. Various other types of research, including chart reviews and simple observational studies, carry less ethical risk. Nonetheless, as in HIC settings, these too require ethical oversight. Given the resource limitations in most LICs, the maintenance of standards to protect research participants likewise remains problematic. Clearly, as pediatric oncology research in LICs expands, exploration of the relevant ethical issues becomes essential.

Moreover, a number of factors give rise to unique ethical issues in pediatric oncology research in LICs. The use of complex, toxic therapies demands nuanced, iterative appraisals of risks and benefits, with resultant implications for study design and implementation. Likewise, the dependence on coordinated, multi-disciplinary care for the survival gains witnessed in HICs implicates the health system as a rate-limiting step for improving outcomes. This underlines the need to evaluate the feasibility and appropriateness of research within variable LIC system contexts, as any perturbation in the system may reduce its ability to deliver care. Lastly, the proven benefits of collaborative approaches in pediatric oncology research in HICs prompt consideration of similar paradigms in LICs, including their attendant ethical issues.

This paper will assess the interplay between pediatric oncology research in LICs and four core issues in the ethics literature: standard of care, trial benefits, ethics review, and informed consent (Table I). We seek to highlight the importance of this field and the need for further inquiry, and to enliven debate on these issues among those involved in pediatric oncology in all settings.

Methods

Literature reviews on ethical issues related to standard of care, trial benefits, ethics review, and informed consent were conducted through electronic searches of major science and social sciences databases (ISI Web of Knowledge, WorldCat, Social Sciences Abstracts, Medline and PubMed), which were supplemented by hand searches of relevant journals and ongoing "snowball" searches from reference lists. We focus on the ethical implications of drug development and intervention research, as distinct from quality improvement projects in pediatric oncology care in LICs. In categorizing countries, we use World Bank definitions of high, middle, and low income countries, with economies divided according to 2008 gross national income per capita (low income, $975 or less; lower middle income, $976–$3,855; upper middle income, $3,856–$11,905; and high income, $11,906 or more) [12].

Table 1. *Ethical Dimensions of Drug Development Research in LIC Paediatric Oncology*

Issue	Themes	Sample questions
Standard of care	Scientific necessity Host community relevance Non-maleficence Host community benefits	What principle(s) should govern determination of the control arm of a paediatric ALL therapeutic trial in LICs?+ What are the social and health system ramifications of the proposed study? What protections should research sponsors and investigators offer to LIC communities in which clinical trials are conducted?
Trial benefits	Reasonable availability Fair benefits	Is provision of post-trial access to the study intervention, if proved safe and effective, mandatory in LICs? Who bears this responsibility? Should researchers employ a different principle to determine the extent and nature of benefits? To what extent should the social context determine the degree or character of trial benefits?
Ethics review	Community engagement Local IRB capacity	What responsibility do international research sponsors/investigators have to create and sustain local IRB capacity? What principles or mechanisms should IRBs use to help research sponsors and communities explore differences in values or perspectives?
Informed consent	Literacy, cultural perceptions of care Agency relationship/ power imbalances Children and proxy decision making	How do researchers and community institutions ensure lack of coercion in trial enrolment? Are any special protections necessary in LICs to ensure protection of the best interests of children enrolled in therapeutic oncology protocols?

Results

Standard of Care–Universalism Versus Relativism

The concept of a "standard of care" has figured prominently in recent debates on international research ethics [13–17]. Defining the "standard of care" is important when deciding which treatment patients assigned to the control arm of a comparative trial will receive; a broader understanding also encompasses disease evaluation, follow-up, and supportive care. Whether or not research trials institute the same standards of care for subjects in LIC settings as they would

for those in HICs is a charged issue with considerable implications for the conduct of pediatric oncology clinical trials in LICs.

The importance of standards of care in medical research is intimately related to the protection of research subjects. Protection, in turn, hinges primarily on the prevention of exploitation. Wertheimer construes exploitation as contingent on the balance between risks ventured and benefits received by each party in a given interaction [18]. Moral discomfort arises from an imbalance in this tally of risks and benefits.

Efforts to guard against exploitation have fostered principles regarding minimum standards of care necessary for the ethical conduct of trials. A prevalent opinion—captured in key pieces of national legislation and international declarations—accords universality to medical standards in research. The US National Bioethics Advisory Commission maintains that "clinical trials (should) provide members of any control group with an established effective treatment, whether or not such treatment is available in the host country" [19]. It defines established as "widespread acceptance by the global medical profession" and effective as "successful as any in treating the disease or condition" [17]. This perspective holds remarkable sway and has fuelled controversy in international collaborative research [14,20–22]. Revised in 2008 in response to ongoing debate on this issue, the World Medical Association's Declaration of Helsinki qualifies the concept of a "universal" standard of care:

The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention, except in the following circumstances: The use of placebo, or no treatment, is acceptable in studies where no current proven intervention exists; or, where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm. Extreme case must be taken to avoid abuse of this option [23].

The Council for International Organizations of Medical Sciences (CIOMS) reaffirms this stance [24]. Growing calls among ethicists, researchers, sponsors, and policymakers for attention to context in standards of care have swung the moral pendulum away from strict universalism toward a conditional relativism in standards for international trials [25–28]. For instance, the UK Nuffield Council for Bioethics explicitly permits modified standards of care for research in LIC settings: "Wherever appropriate, participants in the control group should be offered a universal standard of care for the disease being studied. Where it is inappropriate to offer such a standard, the minimum that should be offered is the best intervention currentlyavailable as part of the national public health system" [29]. The intended goal of relative standards is to minimize exploitation and conduct research of specific value to LIC populations, without shading into outright moral relativism. To this end, Wendler et al. [17] propose that research evaluating less-than-the-best interventions should be allowed only when the following criteria are met: (i) scientific necessity, (ii) host community relevance, (iii) subject and host community non-maleficence, and (iv) sufficient host community benefits.

Scientific necessity implies that an important clinical question can only be answered through use of the proposed control arm. The relevance of this principle to pediatric oncology research is apparent. Consider an LIC institution that has adopted a reduced-intensity treatment protocol for acute lymphoblastic leukemia (ALL), and plans to conduct a randomized trial to determine whether the addition of another agent, such as PEGL-asparaginase, is beneficial. Strict universalism would dictate that the standard arm constitutes an established effective treatment— namely, a regimen deemed optimal ALL therapy in HICs. By contrast, conditional relativism in standards of care allows for a standard arm predicated on the host country's existing treatment protocol—an approach that is not only feasible but provides information of specific value to the population studied. There are, of course, potential problems that attach to such an ethical paradigm, including the perception of double standards and the risk of a persistent gulf in clinical outcomes between HIC

and LIC populations. Clearly, the benefits and risks of relativity in standards of care for pediatric oncology drug trials in LICs need further exploration.

Host community relevance speaks to research that generates findings of clinical value to the local population. In the example above, the control arm most relevant for the host community would be the treatment protocol currently in use, assuming that evidence and experience suggest acceptable toxicity. Conversely, control arms that are impractical in a given LIC setting may lack local relevance and, by extension, ethical credibility. Emanuel et al. [30] have argued that research requires social value to be ethical. A US pharmaceutical company's proposed trial of a novel surfactant preparation against both US-approved surfactant and placebo in Latin American neonatal intensive care units was controversial for this reason [16]. It proposed to evaluate an intervention that was unaffordable in the local settings, against a control that was either unavailable (existing surfactant) or arguably unethical (placebo). The benefits of this trial were directed primarily at HIC populations and were largely irrelevant to local populations. Analogous examples in pediatric oncology are not hard to imagine. The testing of novel and expensive therapeutics (new agent chemotherapies, monoclonal antibodies) are likely not justifiable in populations for whom these interventions would be out of reach before and after the study period.

Non-maleficence in this context requires that research not harm the existing system, nor compromise either the standard of, or access to, current care. Put simply, the trial should not leave the subjects or host community worse off than they would be if the trial were never conducted. Seriously ill children must receive care that is as good as, or potentially better than, existing treatments available to them outside the trial. The research protocol, including its associated infrastructure and trial supports, should maintain or build system capacities rather than drain them. This is a particular risk in LIC settings where individual clinicians and overall health systems confront tremendous workloads. The implementation of a randomized trial in pediatric ALL therefore risks reducing both time for clinical

care and supplies for other patients. Any such trial should therefore hire and train health care personnel, augment laboratory and diagnostic capacity, and improve supportive care for children on therapy to ensure that non-study children do not receive reduced resources or care as a result of the trial's existence.

Trial Benefits

The issue of trial benefits dovetails closely with the "standard of care" debate. Predicating exploitation in research on unfavorable risk-benefit ratios to participants suggests that augmenting benefits works to mitigate potential risks [31–33]. The extent of benefits extended to research subjects and their communities, and the locus of responsibility to ensure their provision, remain pivotal issues. It is now broadly acknowledged that research in LICs prompts a different appraisal of risk, based on a greater potential for exploitation. This compels a distinct and more extensive catalogue of benefits [32,34,35].

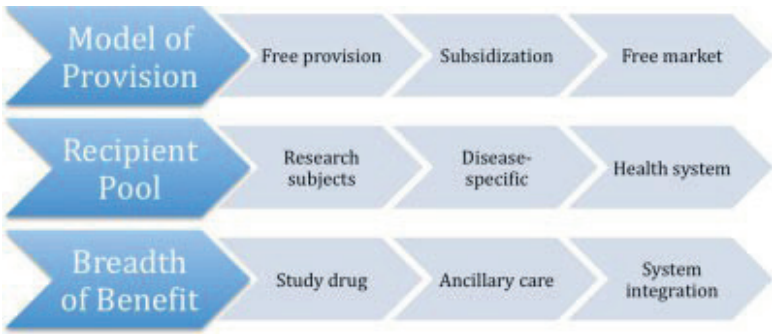
International statements on research ethics, including the Declaration of Helsinki and the CIOMS International Ethical Guidelines for Biomedical Research Involving Human Subjects, demonstrate basic consensus on the issue of trial benefits. Three points are relevant: pre-trial negotiations, intra-trial conduct, and post-trial provisions. Prior to trial initiation, investigators must delineate research conditions and benefits with the host community. At its close, a duty to assure sustained access to effective interventions is assigned. Throughout and beyond, efforts to build local capacity such that host country researchers and institutions can become full partners in the research are required [36]. However, the details of these duties are rarely spelled out and differ across guidelines. Much of the debate revolves around the idea of "reasonably available" benefits. The CIOMS guidelines dictate: "the sponsor and the investigator must make every effort to ensure that any intervention or product developed, or knowledge generated, will be made reasonably available for the benefit of that population" [24]. The Declaration of Helsinki refers to "a reasonable likelihood that (the) population or community stands to benefit from the results of the research" [23].

The vague nature of the duty to ensure that the benefits of the research be made reasonably available leads to debate on several fronts (Fig. 1). First, the nature and strength of sponsors' responsibility to assure post-trial benefits at the outset is questioned. Does responsibility fall squarely on research sponsors and investigators, or is it a shared obligation of all partners, including thehost country or institutions? The means of making interventions "reasonably available" are likewise debated. Are free provision, subsidization, and free market pricing of study drugs equally legitimate ways of discharging this duty? Many research endeavors in the LIC setting are poorly funded and funding is typically limited to the study period. Consequently, continued provision of interventions after study closure may prove difficult, depending on the funding model adopted. Finally, the scope of the recipient pool is unclear. Does this benefit accrue to research subjects alone, or should it include their larger communities?

The study of locally adapted pediatric ALL treatment illustrates these uncertainties. An incremental approach to progress in ALL therapy in LICs implies iterative gains in standards of care. For instance, the successful addition of high-dose methotrexate to ALL protocols in resource-constrained settings depends not only on the cost of the drug but also the system's ability to administer, monitor, and troubleshoot its use. Must investigators, research institutions or local governments continue to fund access to methotrexate at the trial's close? If so, who within the country should have access to it? What about the capacity to provide the supportive care that is needed to safely deliver it? Who bears the longterm fiscal and operational costs for enhanced nursing and laboratory capacity? The responsibility to entrench and extend modalities of supportive care offered on-study—be they medical, such as treatment of chemotherapeutic side effects and opportunistic infection, or social, such as transportation and housing subsidies— to those off-study is far from clear. Most broadly, if study results identify a new standard of care, who is accountable for ensuring that it is made available to the relevant communities?

Despite its acceptance by many guidelines, the concept of "reasonable availability" is controversial. Some regard it as a blunt tool for gauging individual and community benefits, insofar as ongoing access to a trial intervention does not preclude exploitative terms of conduct [37]. In a context of resource scarcity, the strength of the inducement to enroll in research as a means to access the trial intervention may in fact cloud appraisal of a study's risks. It is not hard to imagine a scenario wherein issues of consent, privacy, and risk command less attention than the apparent promise of a study drug, particularly in the context of fatal untreated disease. These issues warrant careful dissection amidst mounting efforts to conduct therapeutic trials in pediatric oncology in LICs.

Figure 1. *Continuum of duty to ensure "reasonable availability" of benefits*



Ethics Review

Formal ethics review board (ERB) oversight is fundamental to the safety and legitimacy of human research. Although routine in most HICs, ERBs are rare in many LICs. Notable efforts have been made to establish ERBs in select LIC contexts [38,39]. Their continued development is crucial to expanded and ethically sound research. However, international collaboration for research oversight is itself fraught with a number of tensions.

Core functions of ERBs include: analysis of the risks and benefits of research to protect subjects and promote equity in the distribution of benefits and burdens; education of researchers; and the audit of ongoing research for public accountability [34]. Although the first of these functions is increasing in LICs, implementation of the latter two remains haphazard. Consequently, both the profession and the public face uncertainty regarding rights and responsibilities in research settings. This has meant more room for exploitation of subjects, blurred lines of responsibility between medical providers, researchers and institutions, and a lack of public accountability for unethical protocols or practices [40].

Community engagement in research design and review— essential to synchronizing research goals, medical realities and community needs—is likewise patchy [41]. The instability of community structures, a dearth of representative institutions, and oversight or rarely willful neglect by investigators are all partially responsible [42,43]. In some countries, a lack of democratically legitimate political structures poses a further challenge. Creative mechanisms for securing robust and sustained channels of communication with local representatives, community leaders, and the interested public are therefore necessary for collaborative research efforts. Enhanced involvement of patient and family voices in the review process through existing or de novo representative bodies, such as local parents' associations, might help meet this need.

The responsibility to establish and maintain local ERB capacity also requires attention. CIOMS and UNESCO guidelines, among others, state that HIC sponsors must aid in the development of ethical oversight of research in LIC settings [24,44]. However, the implications are not well-fleshed out. Are sponsors ultimately responsible for decisions made by host country ERBs in the context of collaborative research? Is autonomy on the part of local ERBs established by foreign investigators realistic, given inherent power imbalances? A host ERB may well feel pressure from its institution to secure foreign research funds and reap the benefits of national and international prestige.

The need to oversee research across differences in culture, health systems, and local medical practices poses particular challenges for collaborative research oversight. Expertise with both the disease and acceptable variance in its treatment are thereforeessential to ethical review of pediatric cancer research in LICs. So too is intimate familiarity with the realities of childhood cancer care in a specific LIC context, if local relevance and feasibility are to be met. Finally, sensitivity to the play of sociocultural factors on perceptions of cancer and its treatment is crucial to the ethicaladjudication of research, especially when considering diseases for which treatment may cripple as well as cure.

Despite the challenges, international collaboration to establish and maintain ERB capacity for pediatric oncology research in LICs can work. Caniza et al. [38] report on the creation of a hospital-based ERB in El Salvador in the context of a twinning program that married the initiative and dedication of local researchers with the practical experience of HIC partners. Its success ultimately spawned El Salvador's first national ERB. However, the maintenance of ERB capacity in El Salvador has proved challenging, suggesting that this and like efforts require ongoing support and collaboration (Raul Ribeiro, personal communication). Nevertheless, the authors construe this as an instrumental component of the duty imposed on international sponsors by CIOMS and other guidelines to improve participant protection in LICs [38].

Informed Consent

A cardinal principle in research ethics, informed consent operationalizes the respect merited by research subjects through formal recognition of their autonomy. A number of issues deserve focused attention in the context of pediatric oncology research in LICs. Some, such as the bind of illiteracy amid provisions for written consent, are more or less easily resolved. The Indian Council for Medical Research guidelines, for instance, contain provisions on admissible verbal consent, witnessed in writing by an unrelated party and potentially documented by audiovisual means, provided confidentiali-

ty is assured [45]. Others, however, have proven more intractable, as they trouble the definition and presuppositions of the concept itself.

The play of social and political power imbalances in global medical research is one such issue. Scarce health care resources, and the consequent incentive for local clinicians to enroll patients in well-funded international drug trials, complicate the process of obtaining truly informed and voluntary consent. Potential role conflicts created by discordant obligations of researcher and physician set this issue in relief. The power inherent in the agency relationship between doctor and patient is ripe for abuse where these identities overlap, particularly so in LICs, where access to care may be otherwise limited.

The ethical course is muddier still with respect to children, over whom another layer of authority is imposed. The issue of proxy decision-making and consent on behalf of children is thorny enough in HICs. The added complexity that stems from research on children in many LICs makes this a uniquely delicate problem. Pressure to enroll children in international drug trials to reap ancillary benefits may hinder informed parental decision making or eclipse consideration of the child's best interests. The inherent risks of this type of coercion are heightened in the context of cancer care, given the physical and psychosocial costs associated with treatment. Conversely, parents or communities unfamiliar with medical research or altogether suspicious of foreign investigators might withhold consent on behalf of their children, despite the latter's best interests, especially when treatment-related morbidity and mortality are so manifest. How to judge the best interests of a child, and who may legitimately do so, are difficult questions. Attempts to square local perspectives with international norms, such as those in the UN Convention on the Rights of the Child, add an additional layer of complexity to this debate. How to resolve the potentially competing needs and perspectives of child, parent, and community in such a setting remains a trying issue in international research, all the more so in respect of interventions as involved, burdensome, and sustained as oncology trials.

Conclusion

Despite far-reaching scientific and clinical advances, vast global gaps in childhood cancer care remain. Research into the nature and extent of these discrepancies and the most effective means of mitigating their burden is essential, as is publication of the methods and results of these endeavors. The unique dimensions of this research demand recognition that the vulnerability of LIC populations to exploitation during drug development research is pronounced; the processes of institutional review and informed consent often weak or uncertain; and the degree of benefit to subjects and communities frequently unclear. The ethics of research into the care of children with cancer in LICs remains largely uncharted territory. Conceptual and empiric testing of questions related to standard of care, trial benefits, ethics review, and informed consent specific to pediatric oncology research efforts in LICs is an essential next step. Only by testing the center and limit of each of these questions against the specific reality of childhood cancer in LICs will we articulate a language up to the task.

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