Paediatric Research in Latin America: Focus on Governance and Populations

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(Article)

Published by NUS Press Pte Ltd
DOI: 10.1353/asb.2015.0014

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Paediatric Research in Latin America: 
Focus on Governance and Populations 

SERGIO LITEWKA* AND KENNETH W. GOODMAN†

Abstract

Research with children is globally subjected to specific safeguards. There are natural aspects related to their cognitive development and their capacity to assent and consent to their participation as subjects. Developing countries, and overall, countries with high levels of inequality due to socio-economic reasons create additional concerns for investigators and research ethics committees members. Several Latin American countries are emerging from decades of political unrest, civil wars and different levels of corruption—situations that are reflected in the number of children living on the street. These children are prone to being used in petty crime, sexual abuse and human trafficking. All research carried out with this particular vulnerable population must adhere to strict ethical safeguards. Although there is no evidence that these minors could be used as subjects in clinical trials, all studies that are to be conducted with these children must respond to specific hypotheses that could ameliorate or even improve their living conditions. The uneven capabilities of local research ethics committees and lax regulatory framework in some Latin American countries are of further concern to this population.

Keywords: research, children, vulnerability, Latin America, street children, clinical research, paediatric research, regulation

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Introduction

Research with children is always controversial. Regardless of the need to discover and study novel therapeutic and diagnostic techniques, clinical and behavioural studies of minors are almost always surrounded by apprehension and, more importantly, concern about how to carry out ethical studies when one of the pillars for research ethics—that participants understand and appreciate the intervention’s risks, benefits and alternatives—is often absent. Most children just cannot grasp appropriate facts and concepts and therefore cannot directly consent to participate. Although adult subjects or participants are sometimes subject to the same concerns, e.g. in emergency or some psychiatric research, investigations with children pose unique and particular concerns.

In the United States, for example, children are given special consideration in federal law. Similar concern and emphasis are reflected in guidelines and regulations in many different countries. Children are perhaps the paradigm exemplar of a vulnerable population. Unfortunately, uncertainty surrounding interventional biomedical research means it can be exquisitely difficult to balance the need to discover new treatments for children and the need to protect them from unacceptable risks. A consequence is that children are not sufficiently represented in clinical trials, and thus many valuable therapeutic and diagnostic alternatives are unavailable for paediatric practice. Challenges posed by such vulnerability are magnified or amplified by the therapeutic misconception, or the unjustified belief that a child will benefit from a clinical trial when standard interventions have been ineffective. A desperate parent, serving as a child’s surrogate for consent, might agree to the child’s participation in a clinical trial even against the child’s best interests. It might, however, be that there are some jurisdictions that are ill-equipped or unnecessary for biomedical research as such. In this case, we should consider the greatest needs of their populations and conduct studies most likely to deliver useful and practical results. These studies are unlikely to involve new drugs for cancer, hypertension or infectious disease.

Shadows of Suspicion

Different countries face different challenges. According to Transparency International (TI), a Berlin-based non-governmental watchdog agency with more than 100 national chapters around the world, corruption is defined as “the abuse of entrusted power for private gain. It hurts everyone who depends on the integrity of people in a position of authority.” Although corrupt practices occur
everywhere, developing countries are at increased risk because of the weakness of those institutions and processes that enforce the rule of law and the mandate of regulations. Every year, TI surveys almost all countries, measuring how average people perceive their relation to the government, the judiciary, political representatives and the enforcement of the rule of law, among several other indicators. It is not surprising that in Latin America, after decades of authoritarian regimes (many of which have been replaced by imperfect and weak democracies), these “Corruption Perception Indexes” are very high. “The CPI ranks countries/territories based on how corrupt a country’s public sector is perceived to be. It is a composite index, drawing on corruption-related data from expert and business surveys carried out by a variety of independent and reputable institutions. Scores range from 0 (highly corrupt) to 100 (very clean)”. Latin American countries, with the exception of Chile and Uruguay, both of which have a score of 73, and Costa Rica at 54, are between the low 20’s and mid 40’s. The United States’ score is 73, Canada 84 and the Scandinavian countries and Australia have scores between 85 and 90.4

Systemic corruption dilutes the moral force and rationale undergirding the rules that govern the life of a society, turning these rules into bureaucratic obstacles that can be ignored in order to achieve a particular result. In countries where corruption is endemic, the organisational and ethical climate of an academic or research institution might be threatened by the prevalence of aberrant attitudes and values that come to be perceived as “normal” or acceptable. This “normalisation” of inappropriate practices allows them to be perceived as minor irregularities (“everybody does it”) and can foster widespread mistrust. Everything falls under suspicion. In all countries and from time to time, scandals related to clinical trials reach the general public. However, in developing countries, in which governance and transparency are questioned, these disclosures are not accompanied by open discussions that could bring more understanding and eventually foster changes in the regulatory framework. If it happens that public disclosure of improprieties leads to the modification of regulations, there are often inadequate resources to ensure enforcement of the new rules.5

Thus, several cases in which Latin American children were involved in questionable research practices generated heated discussion in the region. Unfortunately, ideological biases and, apparently, misconceptions about the meaning of research undermined chances for corrective action.

Some scholars argue that “bioethicists and academics of clinical trials in Latin America have come to the conclusion that researchers working for clinical trials cannot in fact be regarded as researchers since they simply collect data following very specific instructions established in a protocol designed by
industry scientists in other countries." Unfortunately, apparent abuses contributed to the social mistrust on clinical trials. In one instance of a vaccine study of infants at a paediatric hospital in Cordoba, Argentina, parents protested they did not know their children were part of a clinical trial, and that they believed the forms they had signed applied to standard authorisations for immunisation against respiratory diseases. These allegations, coupled with the fact that Cordoba state property was used for private purposes, led Cordoba’s mayor, who had the ultimate responsibility for the hospital, to dismiss the researchers. The investigators appealed the decision, and in 2013 the Provincial Supreme Court ruled that their termination was justified.7

In 2012, the Argentine National Administration for Drugs, Food and Medical Technology (ANMAT) fined a contract research organisation, directed by the same investigator in the Cordoba case, and its sponsor, GlaxoSmithKline, for “irregularities during lab vaccine trials conducted between 2007 and 2008 that allegedly killed 14 babies.” The 15,000 subjects in the phase III pneumococcal vaccine trial—children under the age of 1—were recruited in public hospitals in three Argentinean provinces. Most low-income citizens receive medical care through Argentina’s mostly free public health system. After the children died, their parents, some of whom were illiterate, alleged that they did not know that their children were part of a clinical trial, and, as in Cordoba, that they believed the documents they had signed were conventional authorisations for the vaccination. Also, some parental authorisations were reported to have been falsified. GlaxoSmithKline denied that the deaths were caused by the vaccine,9 but ANMAT stated that the study ignored inclusion criteria and indeed, that many of the children were already suffering respiratory maladies. Moreover, study records were incomplete or absent, and no tests were conducted to determine if the subjects met inclusion criteria.10

**Paediatric Research Ethics in Latin America**

The Latin American subcontinent is a complex mosaic of ethnicities and cultural differences despite the commonalities they share, such as language—mostly Spanish, although Portuguese is spoken in the enormous Brazilian territory, and other indigenous dialects are spoken in the Andean region, the Amazons and the Central American and Mexican countries. Any generalisation will be an oversimplification. Other commonalities are related to politics. These countries share “a past of spotty and disorganised democracy until roughly the turn of the 19th century, when they consolidated their democratic institutions, only to be overthrown—with the exceptions of Mexico, Colombia and Costa Rica—in
the mid-1900s by predominantly, although not exclusively, right-wing dictatorial experiments, occasionally interrupted by weak democracies.”

Civil conflicts affected Guatemala, El Salvador Nicaragua, Colombia, Argentina, Peru and Uruguay between 1940 and 1980. Presently, serious problems persist. The Mexican northern territory, Honduras, Guatemala, El Salvador and some parts of rural Colombia struggle with drug violence, urban gangs and left- and right-wing paramilitary confrontations. As a result, displaced families of peasants are migrating to the main cities, leaving behind their ways of subsistence and trying to survive in urban settings by performing menial tasks in informal economic markets.

Their children are, in many cases, street children, sometimes because they escaped from domestic abuse and in others because the entire family is living on the streets and, in still others, because the minors are orphans or neglected by relatives. Children living in such circumstances are often inappropriate for some or many research studies.

According to the United Nations Children Fund (UNICEF), in Latin America and the Caribbean, 40 million children under 15 years of age suffer violence, abuse and neglect in the family, the school, the community and the street.

We lack reliable data about how many of these children are sought for clinical or psychological studies. An entire generation of South American children emerge as vulnerable not solely because of their status as children; they are hyper-vulnerable because their lives have been shaped by upheaval, neglect or crushing poverty. They are not good candidates for clinical trials.

To be sure, however, and in keeping with the well-accepted rule that research should benefit the community being studied, it is possible that the region's children are suitable for public health and behavioural studies that might shed light on their epidemiologic and social conditions, including under-vaccination, the lack of adequate sanitation and the risks of malnutrition, and abuse or sexual exploitation.

Indeed, because so many South American children are at social risk and lack the basic benefits of public healthcare, we can identify a robust new emphasis for biomedical research. Research ethics in the region should begin both with stricter enforcement of existing laws and adherence to international norms, with an added commitment to broaden the study of problems whose solutions will provide the greatest possible benefit in context. South American children do not need more drug research; high-income countries can shoulder that burden. To be sure, some of the studies advocated here pose difficult questions about how research data will be stored and who will have access to it, how valid consent for sensitive studies will be obtained from this population, and—
especially and perhaps most difficult—how the flawed oversight process reviewed so far can be made to protect paediatric participants and subjects.

For instance, it might be that vaccine safety and efficacy studies are of less value than surveys of vaccination obstacles or adherence rates; that asthma drug studies will help fewer children than will research on childhood exposure to environmental triggers; and that, although treatments for enteroviruses are worthy of study, so is research on the best precautions to prevent the viruses in the first place.

Rather than suggesting that Latin America’s research community ought not to get its house in order, it is these authors’ view that there is a collective opportunity in Latin America to continue to build capacity in research and research ethics while simultaneously fostering vigorous lines of inquiry in support of more immediate and direct benefit to the region’s paediatric population. Consider, for the sake of discussion, that many Latin American research ethics committees suffer from a lack of financial support, and this has impeded acquisition of the kinds of wherewithal needed to approve and oversee risky biomedical paediatric research. If that is the case, then we must advocate both for increased resources, and also for a change of course away from medically risky research—towards behavioural and public health studies offering greater benefits.

Conclusions and Recommendations

Paediatric research will always be difficult, and often is controversial. This is especially the case in resource-limited environments where, for many complex reasons, there are vastly more resources to conduct biomedical research than to educate and support those who have the responsibility to oversee such delicate research. Further, as discussed, Latin America faces great challenges in overcoming research oversight.

Clinical trials with minors are not widespread in developing countries, likely because of a lack of local infrastructure, research governance capacity and ethics competence for dealing with the complexity of this kind of research. Overwhelmingly, most of those (96%) who had participated were in countries with a high or very high Human Development Index (HDI)—a classification developed by the United Nations Development Programme that measures indicators such as life expectancy at birth, level of education and income per capita. All such countries are relatively free of corruption, and the rule of law is strongly enforced. Only 4% of minors were recruited in medium-HDI countries, and none were recruited in the least-developed countries.
Street children, orphans and displaced minors are, unfortunately, a highly vulnerable part of the Latin American population. Any observer in Latin America's capitals will see children sleeping in bus terminals or train stations, performing menial jobs such as shining shoes and washing cars, or simply roaming the streets. The socio-economic conditions that lead to these situations are unlikely to improve in the near future, especially in those countries still suffering from high levels of violence and corruption. Any form of research involving these minors should seek data that could be used to identify, diminish or perhaps ameliorate population-specific risks and risk factors, such as drug use, sexual abuse and sexually transmitted diseases, and exploitation by organised gangs. Optimally, such research might address strategies to identify and evaluate tools to improve the conditions of these populations. Such tools might include expanded education opportunities, adequate preventive and therapeutic medical and psychological care, contraception and other implements to attempt to break the cycle of poverty.

A strong ethical framework is needed for working with this population. Unless such a framework is available—and until legal, regulatory and institutional review challenges are resolved—it might make sense to advocate a moratorium on paediatric research. In the meantime, we have an opportunity to make several positive points, their greatest virtue being perhaps that they should be uncontroversial. A variety of activities could help assure the integrity of research with minors in Latin American countries, including:

- Building capacity not just in the basic human subject’s protection but in identifying and addressing responsibility and accountability of investigators and sponsors. Encourage and fund research of real benefit to the paediatric population. Therefore, expand public health and behavioural research.
- Developing local criteria for protecting children, including insistence on the non-trivial chance of direct future benefit.
- Developing curricula to help regulators and research ethics committees to identify and act on unnecessary or disproportioned risks.

Every continent, it seems, has endured egregious abuses of human subjects in research. All over the world, there exist great challenges in developing and enforcing good practices in health research. The goal is to identify regional impediments and suggest a strategy for improving the health of children by emphasising opportunities, such as those most likely to deliver non-trivial benefits while exposing this vulnerable population to the lowest possible risks.
Notes


