

## ETHICS

# The Ethics of International Research with Abandoned Children

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The aim of human subjects research is to create generalizable knowledge that benefits future patients. Consequently, it risks sacrificing the interests of research participants for the greater good of society. Ethics guidelines exist to minimize this risk. Over the last decade, international biomedical research in the context of substantial health-care inequalities has focused discussion on four ethical issues: (i) standards of care; (ii) informed consent; (iii) ancillary care obligations; and (iv) posttrial benefits (see table, right). It is appropriate to consider these issues relative to the Bucharest Early Intervention Project (BEIP) study (1), a randomized trial of the effects of moving institutionalized young children to foster care.

## Four International Bioethical Issues

The standard-of-care debate erupted in the 1990s around placebo-controlled trials in developing countries of “short-course AZT” for prevention of maternal-fetal HIV transmission. Short-course AZT was expected to be less effective than the standard AZT treatment available in developed countries. Critics argued that using placebo controls, rather than standard treatment as an active control, constituted a double standard—research forbidden on the wealthy would be carried out on the poor (2, 3). Supporters countered that it is permissible to offer research participants in developing countries less-effective interventions than those used in developed countries if doing so (i) is scientifically necessary to answer an important question; (ii) does not deny anyone treatment they would otherwise receive; and (iii) is intended to develop interventions that will benefit the developing country (4).

Informed consent is fundamental to ethical research. But some commentators argue that valid informed consent cannot be obtained in developing countries, whose inhabitants are impoverished, poorly educated, deprived of medical services, and unfamiliar with research (5, 6). Others reply that this is patronizing and inaccurate. Poverty may constrain

choices, but it does not make people coerced or incompetent, and participants in developing countries seem to understand the elements of research as well, or badly, as their wealthier counterparts (7).

Ancillary care refers to medical treatments provided by researchers during the trial above and beyond what is required for safety or scientific validity. Although researchers in developing countries often feel obliged to provide other treatments that their subjects desperately need, the nature and extent of these obligations are

Research with abandoned children does not necessarily involve exploitation.

personnel, employment, and economic stimulation, as well as the study intervention. The total must be considered fair by the community participating in the research (10).

## The Ethics of the BEIP Study

The BEIP was a randomized trial comparing institutional and foster care for abandoned children currently in institutions. It took place in Romania, where there are thousands of institutionalized children. Because, at the trial's inception, Romania lacked basic foster care,

ISSUE	KEY QUESTION	RESPONSE
Standard of care	Must interventions always be tested against the treatment available in developed countries?	Exceptions when scientifically necessary, no harm, and research aims to benefit community
Informed consent	Can poor people in developing countries give valid informed consent to research?	Available data do not show informed consent is invalid
Ancillary care	What treatments should be provided by researchers during the trial beyond those needed for safety or scientific validity?	Depends on the aspects of their health that participants entrust to researchers
Posttrial benefits	What should be provided to research participants and host communities after the research trial?	Two main approaches: reasonable availability of study intervention and fair benefits approved by the community

## Four main ethical issues in international research.

not well defined. The most complete account justifies ancillary care obligations because research participants entrust aspects of their health to investigators through the procedures they undergo (8).

Many believe that researchers have obligations to provide participants posttrial benefits. These benefits are intended to prevent exploitation, which occurs when one party takes unfair advantage of another (9, 10). In international research, the fear is that the developed world will get too much of the benefits of medical research and the developing world too much of its burdens. According to the Council for International Organizations of Medical Sciences (CIOMS), research in a community is permissible only if researchers or their sponsors ensure that interventions resulting from the research are made “reasonably available” to the community (11). An alternative, the “fair benefits” framework, proposes that posttrial benefits may comprise a myriad of benefits including ancillary care, training of health care

the researchers developed their own, training foster parents and providing social support. The study found significantly improved cognitive development at 42 and 54 months for children transferred to foster care before 2 years of age compared with institutionalized children.

The initial reaction to the BEIP may be that the extreme vulnerability of abandoned, institutionalized children renders any research on them unethical. Not only are they unable to give informed consent, there is no clear guardian acting in their best interests. This puts them at greater risk of being selected for reasons of convenience rather than scientific necessity. While these are valid concerns, familiar safeguards can protect such children. People who cannot consent can be protected by enrolling them only in minimal-risk research, whose risks do not exceed those of everyday life. None of the study's assessments of functioning were likely to harm the children. Restricting the participation of vulnerable groups, such as prisoners and the institutionalized, to research that

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addresses important questions relevant to their situation protects against unfair subject selection (12). The BEIP study aimed to produce results that would primarily benefit abandoned, institutionalized children.

The BEIP has many of the features that have generated special concern about medical research in developing countries. Romania, the host country, is a transition economy with a relatively poor health-care infrastructure and a large number of underserved institutionalized children. The funding and research leadership for the trial came from the United States. Although the results may be relevant to the United States and other developed countries, there have been no American randomized trials comparing foster and institutional care, and no American children would be enrolled in the BEIP. Of greatest concern are the standards of care affected in the trial arms and the distribution of posttrial benefits.

The appropriate standard of care for a clinical trial depends on the research question being answered. Although the importance of equipoise, i.e., uncertainty among experts, is disputed (13), ethics requires at least that the research address an important question and be scientifically valid. Trials that do not meet these conditions lack social value. If a research study will not generate socially useful knowledge, it wastes resources and exposes participants to risks and burdens for no good reason.

The BEIP study addresses an important question; the welfare of institutionalized children depends on choosing correctly between further institutional care or switching to foster care. Prior data focused on adoption and did not directly address this comparison, had selection biases, and lacked a definitive randomized trial. Thus, the study appears to fulfill equipoise. Moreover, although both institutional and foster care can sometimes result in maltreatment, study participation was unlikely to cause net harm to the children; no child was put at additional risk to obtain the results, which reduces the ethical reasons for worrying about equipoise.

### Guarding Against Exploitation

To judge whether this trial involved exploitation requires assessing whether the study's benefits were distributed fairly among the parties involved. A useful framework is national research. In a developed country, the results of research are expected to eventually be integrated, albeit haphazardly, into that country's health system. Although participants assume risks in research, they, and their fellow citizens, also benefit. If all subject protection requirements are fulfilled (14), the research is permissible. But in international research, the

people that benefit may not come from the same society as the research participants; no shared national relationship between researchers, subjects, and society exists. Thus, outsourcing research may increase the potential for exploitation.

One way to minimize the chance of exploitation is to emulate national research. According to CIOMS, achieving this in the international context requires that the research be responsive to the health needs of the study population and that the population gains from the research results (10, 11).

The BEIP meets these two conditions. The research responds to the health needs of many abandoned children for whom the state is responsible. Moreover, the instigation of the study by the Romanian Secretary of State for Child Protection and official reaction to its results indicate that the study had a high likelihood of having an impact on these children's lives; state policy was likely to adopt the BEIP conclusions. This impact is not guaranteed: social and economic circumstances or government policies might change, resources may not be made available for foster care, or the conclusions of the research may be disputed. Certainty about implementation cannot be required to ethically proceed with a study. Instead, researchers must judge the likelihood that their work will generate health benefits, and proceed on the basis of its expected benefit. The expected benefits to Romania's abandoned children appear to provide ample justification for the BEIP.

Finally, judging whether exploitation has been avoided by using the responsiveness to needs and reasonable availability criteria can be problematic. These criteria consider benefits to the participants' community. But it is the participants—not the community—who bear the risks of research and are therefore most vulnerable to exploitation. Even when a successful intervention will be available to a population after the trial's completion, supplying it to the research participants themselves may not be possible.

Unfortunately, in many cases harm to participants is inherent in generating valid scientific results. In some trials, data on the effectiveness of an intervention cannot be obtained without some risk to the subjects, perhaps of serious or fatal outcomes. For instance, for a vaccine trial to be successful, some participants must acquire the disease the vaccine is intended to prevent. Otherwise, no intervention can be shown to be superior. But the preventive benefits of the vaccine do no good for participants who became infected during the study. Similar issues arise in many cancer and cardiovascular trials. The BEIP raises the same concern; the children who remained in institutional care

cannot now receive the benefit of early foster care, which the trial showed to be superior for some developmental outcomes.

This consideration does not make the BEIP study unethical, just as it does not make vaccine trials unethical. However, it does indicate that researchers need to pay special attention to how results get implemented when the benefits cannot accrue to participants. For instance, trial designs that move participants into the arm that is doing better during the course of the trial can be employed. According to the researchers, limited funds foreclosed this option. Alternatively, as done in the BEIP, researchers can present valid scientific results as soon as possible to those parties who can act on them. These parties have responsibilities to the participants, too; because the children were involved in research for the benefit of Romanian society, the representatives of society should ensure that the children get the care they deserve.

The BEIP researchers did not create and are not responsible for Romania's institutionalization of abandoned children. They conducted research to determine what interventions would benefit these children. This is not exploitation, but shows how research can help benefit participants, as well as the wider population of abandoned institutionalized children.

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