The Ethical Implications of Clinical Trials in Low- and Middle-Income Countries

Bobbi M Bittker

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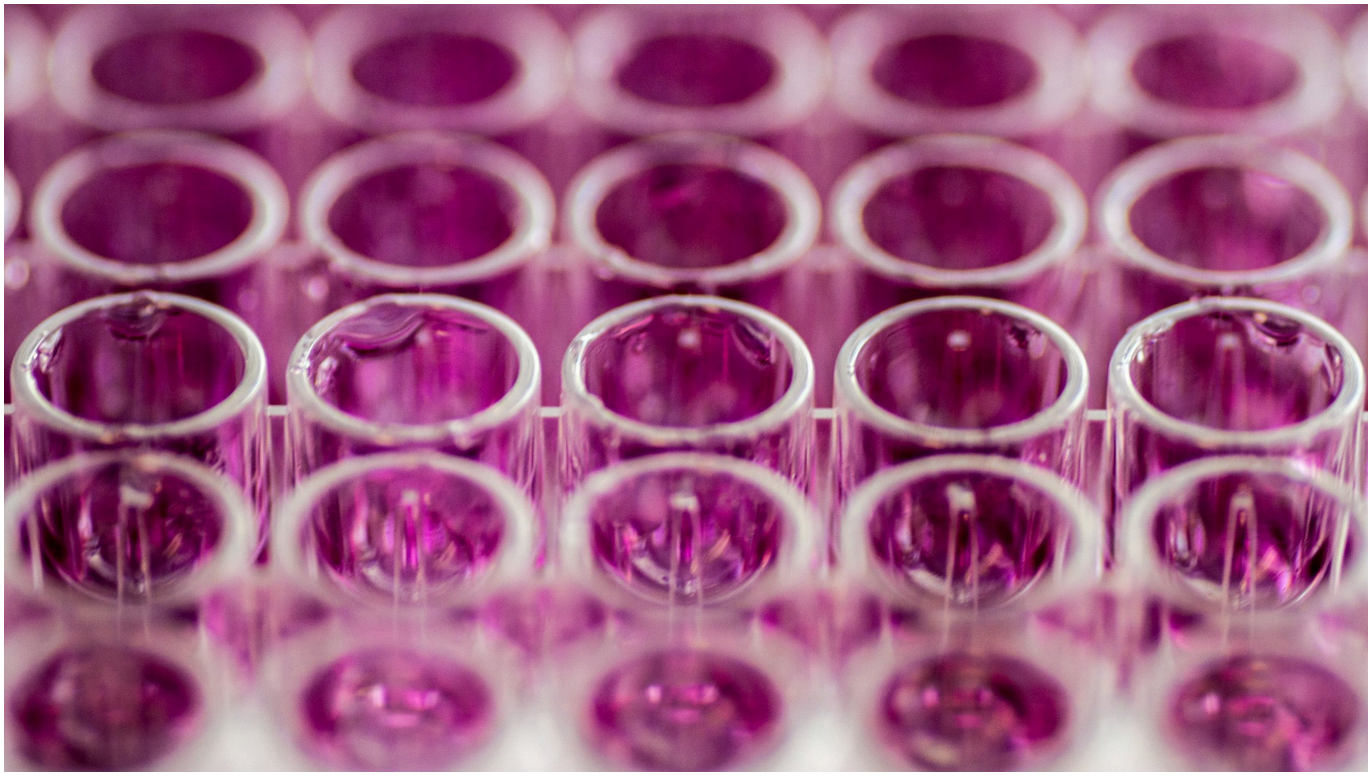
Summary

- Laws, regulations, and ethical standards created to protect human subjects in clinical trials were predominantly reactive to unethical experiments such as the Tuskegee Syphilis Study.
- Clinical trials must follow a framework of seven ethical principles to preserve the human dignity and rights of subjects, including fair subject selection and independent review.
- Health justice requires that all participants in clinical trials benefit equally.



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Medical research has long been performed on human volunteers who risk their own well-being for society's greater good. Safeguarding human rights and upholding ethical standards are fundamental to sound medical research. The globalization of science and medicine relocated clinical trials offshore to low- and middle-income countries (LMIC). Because these communities may otherwise have little to no access to this level of care, are researchers providing a public health benefit or are they exploiting economically disadvantaged communities to serve more affluent ones abroad? Some question whether experimentation is ethical altogether.

The Progression of Clinical Research

There is little debate about which study was the first contemporary controlled clinical trial. James Lind, a ship surgeon in 1747, was alarmed by the high mortality rate of sailors suffering scurvy. One dozen patients with similar cases were placed in the same environment, on similar diets, but given different treatments. He found that those who received citrus fruit were the ones who healed with, by far, the most speed and were restored to the best health.

Over 100 years later, physician Austin Flint treated 13 rheumatism sufferers with an herbal remedy rather than a medical treatment, and he recorded their outcomes. He described this clinical study, the first of its kind comparing an active treatment to a dummy, as the "placeboic remedy."

In 1943, the first modern-era, double-blind comparative clinical trial with concurrent controls was organized by the UK Medical Research Council. They sought treatment for the common cold. Both physician and patient were blinded to the treatment, using an alternation procedure to keep the study strictly controlled. Treatment was dispensed in a discrete room with all identifying information stricken from patient records and treatments.

The first randomized control trial tested the efficacy of streptomycin on tuberculosis in 1946. Subjects were randomly assigned to either the control group (typically receiving conventional treatment) or the experimental group (receiving the regimen being tested). Experimental bias was eliminated here further than in prior clinical trials, patients, investigators, and coordinators all blind to subject placements. Medical providers determined the patients' progress by reading x-rays, analyzing sputum, and reviewing vital signs blind to the identity of the experimental group. Today, we almost universally use randomized allocation in trials.

The Evolution of Protections for Human Subjects

Laws, regulations, and ethical standards created to protect human subjects in clinical trials were predominantly reactive to unethical experiments such as the Tuskegee Syphilis Study or atrocities revealed during the Nuremberg trials.

"Do no harm" birthed a professional ethics code. Yet, as medical treatment became sophisticated, so did its governance. Modern regulation began in 1938, when the United States passed the Food and Drug Act, mandating premarketing safety standards for drugs. This sparked the demand for clinical trials.

Experimentation suffered by prisoners during the Holocaust was revealed at the Nuremberg trials. The Nuremberg Code outlined a canon of ethics, adopted in 1947, requiring informed consent for *only* scientifically necessary medical testing to be performed by qualified personnel. It stressed the autonomy of human subjects and required that humanitarian benefits that result from the research exceed the risks to participants, with the central goal being to prevent human suffering and preserve human dignity.

In 1964, the Declaration of Helsinki was published by the World Medical Association and was revised seven times in subsequent years with additional notes of clarification. Stressing the primacy of the rights and interests of the individual subject, it introduced the concepts of compensation for harm and access to benefits discovered by the research. It specifically addressed the use of placebos and the needs of vulnerable study populations.

Following publication of the scandalous Tuskegee Syphilis Study in 1978, the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research released the *Belmont Report*. The *Belmont Report* specified three ethical principles for the protection of human subjects: Respect: Recognize the autonomy of humans and require clear informed consent; Beneficence: Research must be beneficial and reflect the Hippocratic ideal; and Justice: The benefits to society must be balanced against the risks to participants.

Principles of Medical Ethics on Human Subjects

To preserve human dignity and the rights of subjects, clinical trials must follow a framework of seven ethical principles:

1. **Social and clinical value.** Experimentation exposes subjects to risk, and that risk must be justified. If society and the medical community discover scientific knowledge, the results must be shared and garner enough significance that

warrants asking people to risk inconvenience and unknown health outcomes for the greater good.

2 **Scientific validity.** Studies should be developed to reach clear answers to the query at hand. Is the researchers' question answerable? Are the research methods valid and feasible? Does the study have a clear scientific objective, using accepted principles, methods, and practices? Fallacious research is an unethical waste of resources that exposes people and communities to risk with no greater purpose.

3 **Fair subject selection.** Recruiting for the study should be based exclusively on its scientific goals. Candidate selection should proceed with minimal risk and maximum benefit to individuals and society. Those who accept the risks and burdens of research should be able to enjoy its benefits, and those who may benefit might share risks and burdens. Specific groups or individuals should not be excluded from a study without good scientific reason or particular susceptibility to risk.

4 **Favorable risk-benefit ratio.** Uncertainty about the degree of risks and benefits associated with a treatment being tested is implicit in clinical research. The risks might be minor or considerable, physical, psychological, or social. Clinical research is not being performed to provide health care, but beneficial treatment is often a byproduct. If the benefits outweigh the risks, the research is justified.

5 **Independent review.** An independent review panel, one with no vested interest in the outcome of the study, should review the proposal to ensure its integrity. Are administrators sufficiently impartial? Is the study adequately protecting participants? Is its design ethical and the risk-benefit ratio favorable? In the United States, institutional review boards (IRBs) evaluate and monitor clinical research.

6 **Informed consent.** Individuals must decide, independently, whether to participate in research. This means the subjects are properly informed of the purpose, methods, risks, benefits, and alternatives to the research; they understand the information and how it relates to their own situation and interests; and they decide voluntarily whether to participate. Children and those with limited mental capacity are exceptions to this rule.

7 **Respect for subjects.** It is critical to maintain subjects' confidentiality and abide by their wishes to discontinue participation without consequences when circumstances change. Researchers must share information that arises during the study and inform participants of adverse health effects, although it might change their opinion of the risks and benefits of participation.

Ethical Issues and Clinical Trials in LMIC

Medical research in LMIC raises eyebrows. Self-interested organizers and pharmaceutical companies pursue these communities to capitalize on lower costs, fewer restrictions, and weaker local standards. There is skepticism for good reason. Ethical issues in wealthy countries are amplified in LMIC, where people may not know their rights, and a history of exploitation and racism often exists. Research that 50 years ago was domestic, publicly funded, and reviewed by nonprofit entities is sponsored by drug companies, relocating offshore, and privately funding institutional review boards today. The U.S. Food and Drug Administration (FDA) and government oversight is difficult, if not impossible.

Cultural Differences

Even abroad, American companies must be held accountable by the FDA. The primary goal of conducting clinical trials in LMIC is to address the needs of the local population. Cross-cultural differences may justify different ethical standards. In cultures where individualism is inconsequential, collective decision-making will be a better standard for consent. This "community-based participatory research" asks community stakeholders to participate in the decision-making process with researchers, the ideal being an equal partnership.

Access to Treatment

Clinical trials held in LMIC often result in treatments that the host community cannot afford and often cannot access for decades, even though *they* assumed the burdens. Yet, these studies use local health conditions to learn how to improve public health. How can researchers bridge the gap between the end of the study until treatment becomes available to the host community? Better yet, how can we make the host community among the *first* to benefit?

Public Health

LMIC in Africa, Asia, and Latin America account for a very small percentage of clinical trials. Vaccine research, particularly, requires a population where the disease being investigated is being transmitted in order to establish the efficacy of the vaccine. Responses to the same treatment vary according to factors, including genetics, and Africa is the most genetically diverse continent in the world.

Undue Influence/Exploitation

LMIC communities might be more susceptible to undue influence and exploitation because their socioeconomic disadvantages (need for food and compensation, lack of access to health care) impede their ability to consent freely. Ethical studies focus on the health needs of the host community, so they must be well planned and regulated, and the benefits must be made available to the local community. The Declaration of Helsinki only justifies research in vulnerable communities when "the research is responsive to the health needs or priorities of this group, and the research cannot be carried out in a non-vulnerable group."

Conflicts of Interest

Organizers with financial interests in their sponsoring companies may compromise their professional judgment, neglecting the participants' welfare to increase their own profit. The health and well-being of clinical trial participants are the highest priority, and interests, like monetary gain, can compromise the validity of the research.

Placebos

The Declaration of Helsinki states that the use of a placebo, a dummy treatment, is acceptable where no proven intervention exists, or when compelling and scientifically sound methodological reasons make them necessary to determine the efficacy or safety of an intervention, *and* subjects who receive the placebo will not be subject to risk serious or irreversible harm. The 2000 Declaration of Helsinki update further limited the use of placebos in response to a study about mother-fetal transmission of HIV in LMIC, which denied active treatment to participants in the control group.

In 1997, Public Citizen, a nonprofit, nonpartisan consumer advocacy organization, drew attention to unethical clinical trials, particularly in LMIC. The majority of trials were funded by the U.S. government, and placebos were given to participants rather than researchers using the contemporary standard of care in the United States and other economically similar nations. Unethical research has devastating consequences.

In 1996, an infamously unethical clinical trial was held in Nigeria during a meningitis outbreak. Pfizer conducted a Trovan trial on children without their parents' informed consent. Patients were unaware of the experiment, and the trial was not approved by an ethical review committee. Eleven of the children died, and others suffered brain damage and paralysis.

More recently, in India from 2011–2012, there was a vaccine study to prevent rotavirus, a common but potentially life-threatening viral infection in infants and young children. Despite the availability of two highly effective vaccines that prevent serious rotavirus infections, more than 2,000 children (one-third of study participants) received saltwater placebo injections. The saltwater was not the "best intervention"; there was no compelling scientific reason for placebo use, exposing subjects to risk of a potentially fatal infection; and there was an active treatment available to design a scientifically and ethically sound clinical trial. The use of placebo injections violated international ethical guidelines.

A placebo control group would never have been permitted in the United States, and it should not have been permitted in India. Because of this double standard, Drs. Sidney Wolfe and Peter Lurie argued for a single international ethical standard. Their concern centered around the potential exploitation of communities in LMIC, a majority being people of color. Researchers used substandard care on participants, justifying their decision by citing the "standard of care available" to impoverished host communities as their benchmark.

The Standard of Care Debate

There is a great inequality gap in health care around the world. LMIC communities struggle with access to clean water, badly needed vaccines, and effective medications, unlike their wealthier counterparts where clean water and health care are abundant. The disparities in their living conditions leave LMIC with lower life expectancies and a heavier burden of disease. This drives the debate about which standard of care researchers should apply in clinical trials abroad.

"Best Methods Available"

Harriet Washington, a medical ethicist at Columbia University, says, "In many of these [LMIC], the standard of care is nothing. So it effectively means that trials that would not be permitted here or that at least would undergo a greater ethical furor here can be legally conducted in the developing world." In other words, it is an abdication of duty to provide a community with the standard of care available to them when that standard might be "nothing."

The consensus among ethicists is that IRBs should default to the "worldwide best methods" standard. Some believe there should be exceptions for studies where (1) it is a scientific necessity, (2) it is relevant to the local community, (3) there is a sufficient health benefit to the local community, and (4) there is nonmaleficence; the community will not be made worse by it.

"Standard of Care Available"

On the contrary, the International Conference on Harmonisation-Good Clinical Practice (ICH-GCP) regulation is far more lenient than the Declaration of Helsinki. The required standard of care it applies to the control group depends on the population in the study. That is, control group subjects are only entitled to the standard of care they would otherwise receive locally. If a host community has no access to a particular level of care, the researcher is under no obligation to provide them that care.

Should There Be Clinical Trials in LMIC?

Unethical studies create a dangerous mistrust in public health systems and made the fight to eradicate polio extremely difficult. Today, we are witnessing the same problem in efforts to combat COVID-19.

The African continent, 3.7 percent times the population of the United States, suffered one-fifth the number of COVID-19 fatalities. Good leadership and sound prevention practices were successful. However, Cameroon and Nigeria, countries with good-quality research capabilities, did not participate in vaccine trials, despite past successes in Africa for conjugate meningitis and Ebola vaccine trials. In fact, the African Vaccine Regulatory Forum requires a short (fewer than 60-day) clinical trial approval benchmark. These are valuable opportunities to progress where vaccines need to be tested for safety and efficacy on populations that suffer the diseases. Clinical trials are needed where the newer, more infectious variant of COVID-19 is spreading in South Africa.

Without rigorous information on how vaccines work among African populations in African settings—often with higher rates of comorbidities such as HIV and tuberculosis, conditions favoring more rapid transmission, and more constrained health systems than dominant testing sites—African leaders will be left ill-equipped to make informed decisions on vaccine rollout strategies. When ethical guidelines are followed, along with scientific best practices, LMIC can benefit from local research.

Conclusion

Health justice requires that all participants in clinical trials benefit equally, host community location notwithstanding. One approach is to strengthen ethical guidelines. Another puts the onus on academic institutions, urging them to stress the importance of equitable principles in research. Still, a third way might better protect vulnerable participants from exploitation when wealthy nations conduct their studies in LMIC.

Bioethicist Washington proposes patent law reform to help LMIC that pay high prices for medical treatment they helped develop. Human subjects took risks, and local health care workers conducted the studies, cheaper and more expeditiously than would have been possible in the West. Dr. Washington states, “To me, that means that we’re in their debt.”

Clinical trials are essential to medical advancement. Without them, we would not have eradicated smallpox or have commenced a return to pre-COVID life. Scrupulous researchers rely on individuals willing to bear personal risk for society’s greater good. Self-interested researchers prey on vulnerable populations while flouting best practices. Existing ethical standards must be followed and enforced to achieve health justice, but additional measures will bring us closer to the goal, and all possible steps to protect human subjects must be taken.

Author

Bobbi M Bittker

Bobbi Bittker is a civil rights attorney focusing on legislative policy and advocacy. She is Chair of the Sexual Orientation and Gender Identity Committee of the Civil Rights and Social Justice Section, a member of the Human...