

Narrative Review

Ethical Challenges and Strategies in Conducting Research with Vulnerable Populations in Low and Middle-Income Countries

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Abstract

There is evidence that vulnerable populations (children, prisoners, pregnant women, elderly individuals, and individuals with mental or physical disabilities) have been exploited in the past in the name of medical research. These exploitations were carried out by individuals, institutions and even governments. It highlights the need for mechanisms to protect their rights and well-being. This mini review highlights the landmark events of exploiting vulnerable populations in medical research and outlines measures for their protection. These include the Tuskegee Syphilis Study, the Guatemala Syphilis Experiment, and the Holmesburg Prison Experiment. These well documented examples from the past suggest that there is a need for establishing and following a framework ethical guideline, obtaining informed consent, and reducing risks to the research participants. Protection of the vulnerable populations require that researchers must follow ethical standards, such as those recommended in the 1979, Belmont Report. These principles include respect for persons, beneficence, and Justice. An appropriate mechanism for a formal and truly Informed consent from the research participants and appropriate approval and oversight of Institutional Review Boards/ Ethical Review Committee (IRBs/ERC) are necessary to ensure that the research is being conducted in an ethical manner. Individual researchers and medical institutions should also consider the potential exploitation of the vulnerable populations during the research process. They must consider additional safeguards while conducting research into populations that are considered vulnerable. These steps are an ethical and moral obligation for the researchers to avoid exploitation of vulnerable populations in the name of scientific research and to safeguard their interest. These steps can ensure that the medical research is being conducted in an ethical manner and is likely free from exploitation of the research participants. As a result, the outcomes of such research can be trusted to make correct medical practices and policies.

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Introduction

Vulnerable populations in medical research is defined as groups of people (potential research participants) who may be at an increased risk of being exposed to unnecessary harm or exploitation during



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the research process. Hurst suggests that vulnerable population are those who have “an identifiably increased likelihood of incurring additional or greater wrong”.^{1,2} The vulnerable populations may include a variety of groups. These many include but, is not limited to children, prisoners, pregnant women, elderly individuals, and individuals with mental or physical disabilities. These groups are at increased risk of being coerced into participating in research, manipulation, or other forms of physical or mental abuse.³ Vulnerability of an individual or groups in medical research also depends on the context and sociocultural background. It is possible that individuals may be considered as vulnerable in one context and not the other.⁴ For example, research participants from resource-limited areas and Lower Middle Income Countries (LMIC) who are offered a large financial incentive to participate in a high risk research can be considered as vulnerable. However, the same individual may not be considered at risk or vulnerable when participating in a research survey without any financial compensation and after taking a fully informed consent.^{4,5} It is important to identify and devise mechanism to protect vulnerable populations in medical research at the start and during the process of research, as these groups may face a greater risk of research related harm or exploitation due to their circumstances or characteristics.⁴ There is a need to identify and consider the vulnerability of these populations when conducting medical research in order to ensure that their rights and well-being are being adequately safeguarded. This narrative review addresses historical abuses involving vulnerable populations and explores how these vulnerabilities persist even today in LMICs in international clinical research. Additionally, it highlights the importance of protecting these populations not only in global studies but also within local research frameworks and advocates for the creation of culturally and contextually specific protocols. The paper concludes by providing recommendations to enhance protections for these populations in Pakistan.

Historical Perspectives on the Exploitation of vulnerable populations in medical research:

Exploitation of vulnerable populations in medical research refers to the abuse or misuse of these individuals for the purposes of research. This can take

various forms, including failing to obtain informed consent, using deceptive or coercive tactics to enroll individuals in research studies, or exposing them to unnecessary risks or harms. There have been numerous well documented historical examples of the exploitation of vulnerable populations in medical research. In the past, many research stakeholders including individual physicians, researchers, scientists, institutes and governments have experimented upon their patients or enrolled them in high risk research without their knowledge, consent or mechanism for compensation. Some of the most well-known examples include:

1. **Origins of Modern Gynaecology:** Dr. James Sims, known as the "father of modern gynecology," developed gynecological instruments and refined surgical techniques for repairing vesico-vaginal fistulas by experimenting on enslaved Black women without their consent.^{6,7}
2. **The Tuskegee Syphilis Study:** This study conducted by the United States Public Health Service from 1932 to 1972 involved 600 African American men who were intentionally left untreated for syphilis, despite the availability of effective treatments.^{8,9} The subjects of the study were not informed of the true nature of the research and were not provided with adequate treatment or follow-up care. This study is widely considered to be a grave violation of ethical principles and has had long-lasting effects on the trust of minority communities in the research process.
3. **The Guatemala Syphilis Experiment:** The United States Public Health Service conducted this unethical research from 1946 to 1948 in Guatemala (a poor country). In this government sponsored study prisoners, mentally challenged patients, and soldiers were deliberately infected with syphilis and other sexually transmitted diseases without their consent and knowledge.¹⁰ The researchers did not disclose the true nature of the research to the participants. The participants were not provided with adequate treatment or follow-up care for the issues arising due to participation in research, since the aim

was to study the natural course of the disease-syphilis. This study has been widely condemned as a serious breach of ethical principles.

4. **U.S. government-sponsored radiation research on humans:** These experiments, conducted by the U.S. government from 1945 to 1975, exposed hundreds of USA citizens to various forms of radiation. A 1986 report titled "American Nuclear Guinea Pigs: Three Decades of Radiation Experiments on U.S. Citizens" revealed that the subjects were often unaware they were part of high-risk research and, in most cases, were not compensated for the harm caused by radiation exposure.^{11,12}
5. **The Holmesburg Prison Experiment:** Between 1951 and 1974, prisoners at Holmesburg Prison in Philadelphia, USA were subjected to experiments involving exposure to various toxic chemicals and hazardous substances, including that including dioxin, radioactive isotopes, and sarin gas.¹³ The study participants were not fully informed of the nature of the research, or the risks involved. As a result, many research participants developed serious health problems which were directly attributed to their enrollment in this unethical research.

The Council for International Organizations of Medical Sciences (CIOMS) published the "International Guidelines on Good Governance Practice for Research Institutions" in 2023.¹ These guidelines provide detailed and specific guidance for research institutions to implement existing standards and best practices, facilitating the conduct of ethical and high-quality scientific research. These guidelines are essential for institutions aiming to uphold the highest standards in research governance.

Recognizing the inherent vulnerability of certain populations in medical research is necessary so that appropriate steps can be taken to protect their rights and well-being. This can ensure that medical research is conducted in an ethical and transparent manner and that the results of these studies can be trusted to guide medical practice and policy.

Strategies and Mechanisms for Protection of the vulnerable population in LMIC

Conducting research involving vulnerable

populations presents distinct challenges in low- and middle-income countries (LMICs) compared to high-income countries (HICs).

Socioeconomic and Operational Challenge

In LMICs, pervasive poverty, limited access to healthcare, and lower levels of education can exacerbate participants' vulnerability. The individuals participate out of necessity rather than genuine consent and they might not receive adequate medical care outside the study context, raising ethical concerns about beneficence and justice. Bruce AA, et al reported unique challenges of vaccine clinical trials in Gambia. Healthcare-seeking behaviors limited diagnostic tools, and low literacy of participants impacted the accuracy of adverse event reporting. These were addressed by strategies such as self-treatment prohibition, round-the-clock patient care and establishment of clinical services department for the participants.¹⁴

Regulatory and Ethical Oversight

IRBs in HICs may lack understanding of local contexts in LMICs, leading to culturally inappropriate recommendations. Ethical review processes in LMICs can be complex and may involve multiple institutional review boards (IRBs) from both sponsoring and host countries. Moreover, Biomedical researchers trained in high-income countries faced challenges when reintegrating into LMICs, due to the lack of local infrastructure and expertise as reported by Ahmed et al.¹⁵

Cultural and Social Considerations

Cultural differences can influence perceptions of autonomy, consent, and vulnerability. In some LMICs, communal decision-making may prevail over individual autonomy, complicating the informed consent process. Additionally, social hierarchies and power dynamics can affect participants' willingness to refuse participation, raising concerns about voluntary consent. Vulnerability should be addressed for an individual as well as one of the environment or research protocol factors. Victor E et al have reported interplay between these factors as layers of vulnerability.¹⁶

The Medical Research Council (MRC) Unit Gambia at London School of Hygiene and Tropical Medicine collaborated a recently completed Expanded Program on Immunization Consortium (EPIC) study in 2021. This study was a collaborative effort in USA, Canada, Belgium, Papua New Guinea, and Gambia. The study enrolled and followed up with 720 newborns in two years. They shared field experiences, highlighted operational challenges and reflected on the study's implementation. The EPIC team faced challenges including limited in-country specialists, logistical issues, participant recruitment difficulties, host health facility constraints, and rumors about the study. They addressed these by recruiting regional experts, using a specialized transport system, expanding recruitment to other facilities, reorganizing staff, constructing an office complex, providing training, and implementing a community communication strategy.¹⁷

While vulnerable populations in HICs also face challenges, the context differs. HICs generally have stronger regulatory frameworks, better healthcare infrastructure, and higher levels of education, which can provide additional safeguards for research participants. However, issues such as socioeconomic disparities, racial and ethnic minorities, and marginalized groups still present ethical challenges in research within HICs.¹⁸

Perspectives from the developing world- Case of Pakistan

In low- and middle-income countries (LMICs) like Pakistan conducting human subject research can present some unique ethical challenges, particularly regarding the protection of vulnerable populations.

1. **Issue of Informed Consent:** In Pakistan, Individuals are considered vulnerable when their capacity to safeguard or advance their own interests is compromised. This can be due to cognitive (lack of education) or communication (language barriers). Further, informed consent challenges needs to be addressed in power differential settings (prisoners, nursing home residents, old homes, madrassas and students). Other factors include low socioeconomic status and limited access to healthcare. The principle of

justice recommends equitable distribution of the benefits and burdens of research. Disadvantaged and vulnerable populations should not be preferentially recruited as participants if other groups could also appropriately address the research question. Conducting research with vulnerable groups primarily because they are easily accessible, compliant, and have reliable follow-up opportunities exploits their circumstances unfairly. This limits the ability of participants to fully understand the implications of their involvement in research. Therefore, it is common to see the participants just signing the form without even reading it.

2. **Power Differential and Hierarchy:** There is often a power imbalance between researchers (mostly treating physicians) and participants (usually patients reporting for treatment), which is further exacerbated by socio-economic disparities. For instance, studies have shown that individuals from low socio-economic backgrounds may feel pressured to participate in research due to the incentives offered, such as free medical care or financial compensation, raising concerns about coercion. Researchers should clearly explain the nature of the research, risks and benefits. In addition, they must ensure an ethical study design so that potential risks or harms are minimized
3. **Social and Cultural Norms:** The cultural and social norms in Pakistan can also negatively influence the recruitment of research participants. For example, women, may face cultural barriers due to societal norms that limit their autonomy and decision-making power. It is common to see men (father, husband, brother or son) giving consent and signing the consent form on behalf of the women without even consulting them while they are also present. Pakistan has a culture where family relationships are prioritized over individual liberty. Therefore, decisions like informed consent may be viewed as collective particularly when it involves children and women. Privacy and respect may have different cultural connotations here. Researchers from affluent countries must be aware of specific cultural considerations when conducting cross-

cultural research in LMIC. A collaboration between the Pakistan Institute of Living and Learning and University College London explored local cultural values in Pakistan to inform a cultural protocol for researchers from high-income countries, identifying key themes such as religious principles, autonomy, respect, cultural etiquette, and tradition. Such efforts build research capacity in LMIC that pose cross-cultural communication challenges.¹⁹

4. **Weak Ethics Regulatory Framework:** The research ethics regulatory framework in Pakistan is still evolving. The Pakistan Medical and Dental Council and the National Bioethics Committee provide some guidelines for ethical research that are available on their respective websites. However, on ground implementation of these guidelines is inconsistent and questionable. In addition, institutional oversight of the research process is often inadequate due to multiple factors. Experts have pointed out that many IRB and ERCs around the country lack the necessary expertise and resources to thoroughly evaluate research proposals. This potentially leads to ethical oversights and IRBs which are labelled as 'rubber stamps'.²⁰ This situation is further complicated by the fact that most of the healthcare professionals and researchers in Pakistan do not receive a standardized training in research ethics either at the undergraduate or postgraduate level. Therefore, ideally an IRB should be composed of a diverse group of individuals from different backgrounds (including non-physicians, patients representative and a lawyer) with relevant expertise and experience.²¹

It is important to note in the context of developing countries like Pakistan, ethical considerations and safeguarding vulnerable population in research will require a pragmatic and multifaceted approach. It is not possible to copy and adopt the approaches used in the West and the developing countries with robust ethics oversight and well-established research culture. The possible strategies may include improving public awareness about the importance of ethical research practices and the rights of the research participants and strengthening the capacity and authority of IRB/ERC. It is also important to

provide comprehensive and formal training to the researchers in research ethics at various stages. Other strategies include active community engagement and culturally sensitive communication strategies in order to build trust and to ensure truly informed consent for enrolment in research. Addressing these and similar challenges is important to ensure that the research conducted in Pakistan and other LMIC is ethical and free from exploitation of the vulnerable populations.

Conclusion

Protecting vulnerable populations in medical research is an important consideration, because these groups are more susceptible to be abused or exploited because of their social, economic and cultural circumstances. This protection can be offered in many ways, such as by strictly adhering to the ethical standards and guidelines, appropriate informed consent procedures, and approval and oversight by the institutional review board. Researchers, physicians, medical institutes and research organizations must be aware of the risk of exploitation or harm to the vulnerable populations and to take necessary steps to reduce or eliminate this risk.

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FAR: Conception and design, literature review, drafting the manuscript, final approval of the version to be published.

FF: Conception and design, drafting the manuscript, revising it critically for important intellectual content, final approval of the version to be published.

TWM: Literature review, revising it critically for important intellectual content.

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