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**Review Article**

# Navigating the global shift: prospects and challenges in the clinical research enterprise

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## ABSTRACT

In recent years, the conduct of clinical trials in developing countries has increased markedly, reflecting a broader shift of the clinical research enterprise toward non-traditional geographic regions. This expansion is driven by multiple factors including greater availability of research participants, decreased costs of conducting research and, in some cases, less restrictive regulatory environments. While these underlying forces present valuable opportunities to the clinical research enterprise system, they also introduce complex scientific, ethical, and regulatory challenges. Nevertheless, if the challenges are navigated prudently, the globalization of clinical research trials may hold considerable potential to accelerate the development of innovative medical therapies that could contribute meaningfully to addressing the global health needs.

**Keywords:** Clinical trials, Developing countries, Ethical challenges, Globalization, Infrastructure, Regulatory framework

## INTRODUCTION

Globalization is a pervasive phenomenon that has significantly impacted virtually every sector, albeit to varying degrees. While globalization represents a relatively new dynamic for certain industries, others, such as health care, have engaged with its principles for a longer period. Nonetheless, it is evident that globalization has gained considerable momentum in the health care sector in recent years, a trend largely driven by the escalating global burden of disease and the emergence of new infectious outbreaks.[1] These developments have necessitated a more proactive and coordinated international response, mobilizing multiple branches within the health care system to address the rapidly evolving public health challenges.

One critical branch at the forefront of this global response is research and development (R&D). Through R&D initiatives focused on pharmaceutical products and medical devices, new therapies and technologies are introduced to the market. However, before market entry, it is imperative to rigorously establish the efficacy and safety of these innovations through clinical research.[2] Clinical research involves studies that prospectively assign human participants or groups to one or more health-related interventions to assess health outcomes.[2] This process of evaluating new healthcare interventions new medical products may be costly, lengthy, and complex, given the intricate scientific, ethical, and regulatory requirements that must be met.[2]

Historically, clinical trials were primarily conducted within developed countries.[3] However, with the increased desire to explore new geographic opportunities, there has been a marked expansion of these trials to international locations, particularly in Asia, India, and Africa.[3] These expansion has brought numerous benefits which include; accelerated drug development, reduced costs, greater accessibility to research participants, and, in some cases, less stringent regulatory environments.[3] Conversely, these expansion of clinical trials have also been faced with a

host of complex challenges such as; ethical predicaments, cultural differences, regulatory variability, and infrastructural limitations.[4] It's because of the opportunities and challenges associated with clinical trials that this article intends to examine the historical evolution of clinical research and its subsequent globalization while reviewing the driving forces behind the globalization of the clinical research trial enterprise. Additionally, this article will discuss some of the challenges and ethical dilemmas associated with globalization and the potential strategies aimed at addressing these complex issues.

## HISTORICAL BACKGROUND

The history of clinical research can be traced back to antiquity. However, it was not until 1747 that James Lind conducted one of the earliest recorded systematic clinical trials, investigating potential treatments for scurvy.[5] Lind's work marked the beginning of a series of significant milestones in the evolution of clinical research. Notable early achievements include the coining of the term placebo in the 1800s and the first double-blind controlled trial, the Patulin trial for the common cold in 1946, which subsequently paved the way for the first randomized controlled trial assessing the efficacy of streptomycin for tuberculosis.[5] In the subsequent decades, clinical research witnessed numerous advancements, particularly in the areas of ethical oversight and regulatory frameworks.[5] Of note is the Hippocratic oath an ethical underpinning of human subject protection.[5] Despite these early ethical interventions, there were still gaps in the clinical trials conducted in the early years. In response to widespread abuses, a series of landmark ethical and regulatory frameworks were established. One of the most significant was the Nuremberg Code, formulated in 1947 in response to the atrocities committed during the Nazi experiments and the Tuskegee syphilis study.6 The Nuremberg Code emphasized the necessity of voluntary consent and laid the foundation for modern research ethics.[6]

The other major development was the Declaration of Helsinki, adopted in 1964 by the World Medical Association.[6] This document articulated a set of ethical principles specifically for medical research involving human subjects and has since undergone multiple revisions to strengthen its protective standards.[6] The third key milestone was the Belmont Report, published in 1979, which established three fundamental ethical principles to guide research involving human subjects: respect for persons, beneficence, and justice.[6] The Belmont Report has played a critical role in shaping contemporary ethical standards for human experimentation. In addition to these ethical milestones, certain events further influenced the regulatory landscape. Notably, the thalidomide tragedy of the 1960s, in which the use of thalidomide as a sedative for pregnant women led to severe congenital deformities, catalyzed significant regulatory reforms.[6] Public outrage over the insufficient safety testing of thalidomide prompted legislative action in the United States, culminating in the passage of the Kefauver-Harris Amendments, which mandated stricter safety and efficacy testing for new drugs.[7]

Despite the establishment of robust ethical and regulatory mechanisms, the globalization of clinical research introduced new challenges, particularly concerning the variations in ethical standards and regulatory practices across countries.[8]

To address these discrepancies, the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) developed the ICH E6 Guidelines: Good Clinical Practice (GCP).[8] Approved on July 17, 1996, and implemented globally beginning January 17, 1997, the E6 Guidelines established unified standards for the design, conduct, performance, monitoring, auditing, recording, analysis, and reporting of clinical trials.[8] Since then, the ICH-GCP framework has remained a cornerstone of international clinical research practice, ensuring the protection of human subjects and the credibility of clinical trial data worldwide.

## BENEFITS OF CLINICAL RESEARCH GLOBALIZATION

Clinical research represents a critical stage in the development of new pharmacological and medical device products, as it enables the evaluation of their efficacy and safety. Traditionally, clinical trials were conducted predominantly in developed countries. However, this trend has shifted dramatically in recent years, with a significant expansion of clinical research activities into developing regions.[1] Some of the factors that have contributed to this trend include easier access to research participants, flexible regulatory framework, and significant economic incentives.

### *Access to research participants*

One of the primary drivers of clinical trial globalization is the relative ease of recruiting participants in developing countries. The success of any clinical trial is heavily dependent on the availability of eligible subjects. In contrast, subject recruitment remains one of the most significant challenges in developed countries.[9] Notably, over 8% of global clinical trials fail due to inadequate participant enrolment, a trend particularly pronounced in industrialized nations where most R&D companies are based.[9] Recruitment difficulties can result in prolonged trial timelines, increased costs, and compromised study credibility.[9] In some cases, insufficient enrolment even leads to premature trial termination, delaying potential breakthroughs in therapeutic innovation.[9] To mitigate these challenges, pharmaceutical companies, medical device manufacturers, and research institutions have increasingly turned to developing countries, where large, diverse patient populations are more readily available.[9]

Factors contributing to high enrolment rates in developing countries include the appeal of access to trial medications and the financial incentives offered to participants.[9]

### *Flexible regulatory frameworks*

A second factor influencing the globalization of clinical research is the relative flexibility of regulatory frameworks in many developing countries.[9] In industrialized nations, clinical research regulations are often complex and can significantly delay the approval of research protocols and the subsequent introduction of new drugs to the market.[9] By contrast, the regulatory environment in many developing countries is less rigid, allowing for faster protocol approvals and facilitating a more expedient research process.[9] This regulatory agility makes developing countries attractive locations for clinical research, offering pharmaceutical companies an opportunity to accelerate the development timeline for new therapies.

### *Economic considerations*

Economic factors also play a pivotal role in the globalization of clinical research. Currently, the average cost of bringing new medication to the market is estimated at $2.6 billion over a period of 10 to 15 years.[10] The escalating costs associated with R&D in developed countries have created a significant deterrent to innovation. To reduce expenses, pharmaceutical companies are increasingly outsourcing clinical trials to developing countries, where operational costs are substantially lower.[10] These cost savings are largely attributable to lower salaries for clinical research personnel, reduced overhead expenses, and shorter participant enrolment periods.[4] By contrast, in developed nations, higher salaries and operational costs can substantially erode profit margins hence leading to less desire to pursue clinical trials in these geographic locations.[4]

## CHALLENGES ASSOCIATED WITH THE GLOBALIZATION OF CLINICAL RESEARCH

While the globalization of clinical research presents numerous opportunities, it also introduces a host of challenges, particularly when trials are outsourced to developing countries. Key concerns include ethical dilemmas, cultural and language barriers, variable regulatory standards, and issues related to infrastructure and oversight.

### *Ethical concerns*

#### *Standard of care*

One of the principal ethical concerns associated with the globalization of clinical trials is the questionable standard of care provided to research participants in developing countries. Internationally, there is a consensus that clinical trial participants must receive care that does not compromise their safety.[11] However, in practice, this remains a contentious issue, particularly in low- and middle-income countries (LMICs), where participants may receive substandard care both during and after trials. The debate over the standard of care dates back notably to the 1997 controversy surrounding AZT trials, wherein participants were administered a placebo rather than a proven therapeutic intervention.[11] This controversy raised global awareness and prompted calls for stricter adherence to ethical guidelines mandating that research participants receive the highest possible standard of care, including proven, current, and effective treatments, irrespective of geographic location.[12]

Two critical issues emerge regarding the standard of care in developing countries. First, the ethical acceptability of using a placebo or withholding known effective therapies for control groups remains contentious, particularly given the heightened risk of exploitation in LMICs.[12] Second, the overall standard of care available within these countries is often compromised by fragile healthcare systems, making adherence to international best practices challenging.[12] However, the UNAIDS guidelines emphasize that the highest available standard of care within the host country should be the minimum threshold of the standard of care even though systemic healthcare deficiencies frequently tend to impede compliance.[12]

### *Social value*

Another significant ethical concern is the limited social value that research often brings to host communities in developing countries. Based on the Declaration of Helsinki, researchers are ethically obligated to inform participants of study outcomes and, where appropriate, provide them access to proven interventions.[13] Furthermore, the broader community should also benefit from the research findings and failure to do so can result in perceptions of exploitation, where LMICs bear the risks of research while the benefits accrue primarily to populations in high-income countries.[13] Moreover, there is also the challenge of ensuring that post-trial treatments are accessible to people in the low income countries.[13] One of the reasons that has been put forward for the hesitancy of pharmaceutical companies to extend such access to low income countries is the prohibitive costs of medications.[13] And because the post treatment access is limited, these trials have been widely regarded as exploitative, particularly in settings where alternative treatments are unavailable.[13]

To address these issues, several measures that have been recommended include articulating the prospective social value of the research to participants prior to enrolment; and mandating research sponsors to provide post-trial access to effective treatments for a reasonable period, allowing participants sufficient time to transition to alternative care.[13]

***Informed consent***

Informed consent is a foundational ethical requirement in clinical research and practice. Its purpose is to ensure that participants understand and voluntarily agree to the potential risks and benefits of participating in a study.[14] Nevertheless, obtaining valid informed consent in developing countries presents unique challenges. First, socio-cultural dynamics, including paternalistic societal structures, often limit individual autonomy.[15] Participants may feel unable to refuse participation due to deference to authority figures or community leaders, leading to communal rather than individual consent.[15] Often this may lead to community interests superseding individual rights. Second, low literacy levels impede participants' comprehension of complex medical information.[14] Consequently, individuals may consent without fully understanding the nature, purpose, and risks of the research. Third, language barriers may further complicate the informed consent process more especially when trial materials are written in English and there is no lack written forms, and clinical trial materials written in English.[15]

To strengthen the informed consent process, several strategies are recommended which include collaborating with local communities to design culturally appropriate consent processes, disclosing information in local languages using culturally resonant idioms and analogies and lastly employing certified interpreters and utilizing alternative communication methods, such as recorded messages or visual aids, to convey study information.[17]

***Undue influence***

Undue inducement is a critical ethical concern, particularly in settings characterized by high levels of poverty. This practice entails offering financial or other incentives that are so substantial that they risk compromising the participants' ability to make rational, voluntary decisions, leading them to underestimate risks or overestimate potential benefits.[18]

Monetary compensation is known to positively influence participation rates; however, excessive incentives may impair judgment, resulting in ethically problematic enrolment decisions.[19] In LMICs, the threshold for undue inducement is particularly low due to widespread economic deprivation.[4]

To mitigate undue inducement, all proposed participant compensation must be reviewed and approved by ethical review boards. This oversight ensures that payments are fair, do not compromise voluntary participation, and uphold the ethical integrity of the research.[18]

***Regulatory concerns***

*Ethics committees*

Ethics committees play a vital role in safeguarding the rights and welfare of research participants by rigorously reviewing clinical trial protocols. However, in many developing countries, the regulatory framework is weak, and researchers sometimes circumvent ethical review processes. For example, studies have shown that 90% of published clinical studies conducted in China did not document ethical review, and informed consent was inadequately addressed in many cases.[20]

Several factors contribute to the inefficiency of ethics committees in LMICs, including resource constraints, complex approval processes, and lack of expertise among Institutional Review Board (IRB) members.[1,21] Moreover, cultural unfamiliarity can result in ethical standards that are not adequately aligned with local contexts.[1]

To enhance the effectiveness of ethics committees some of the measures that have been suggested including establishing robust ethical frameworks that foster collaboration among stakeholders, offering continuing education for IRB members through workshops and seminars, promoting multidisciplinary committee membership and striving for financial independence to ensure impartiality and sustainability.[9,22]

***Corruption and transparency***

Corruption and lack of transparency represent additional regulatory challenges in the globalization of clinical research. In environments where corruption is systemic, the integrity of clinical trials is at risk.[23] Corruption costs Africa an estimated $148 billion annually, and similar patterns are observed in Russia, India, and Thailand, where bribes are sometimes solicited in exchange for trial approval.[23]

Corruption can lead to fabricated data, compromised participant safety, and erosion of public trust.[24] Moreover, it undermines the training of future scientists, perpetuating a cycle of unethical research practices.[24]

For credible clinical trial outcomes, transparency is critical to foster public trust.[25] Measures to enhance transparency include developing globally harmonized regulatory databases, mandating trial registration, and closely monitoring foreign research ethics boards.[25]

***Infrastructural concerns***

*Poor physical infrastructure*

For a clinical trial to be successful, the interplay of multiple factors is essential. One of the less frequently discussed yet crucial elements is the physical infrastructure supporting the trial. Infrastructure encompasses elements such as adequate office space, dedicated investigational product and study drug storage areas, deep freezers for biological sample storage, reliable power backup systems, document archiving facilities, institutional biobanks, among others.[25] While such resources are typically available in developed countries,

infrastructure in many developing countries remains insufficient, thus impeding the timeliness and overall effectiveness of clinical trials.[25]

According to the United Nations Conference on Trade and Development's (UNCTAD) latest Economic Development in Africa Report, only one percent of global manufacturing occurs in Africa, largely due to inadequate transport, communication, and energy infrastructures.[25] Although Africa and parts of Asia continue to attract clinical research due to factors such as lower costs and diverse populations, poor infrastructure remains a major challenge to conducting trials efficiently.[25]

To address these infrastructural shortcomings, research organizations that outsource clinical trials to developing countries should establish robust partnerships with international vendors, thus mitigating logistical challenges and ensuring smoother trial operations.[25]

*Technological challenge*

A related infrastructural concern in developing countries is the prevalence of technological challenges. Technology has significantly advanced clinical research by facilitating data sharing, real-time monitoring, and efficient management of clinical trials.[26] However, in many developing countries, limited technological infrastructure hampers the ability of research teams to share data and monitor trial progress, particularly in remote locations.[26] Notably, technology is critical for achieving measurable improvements in clinical research, such as expediting study start-ups, streamlining data transmission, and enhancing study monitoring processes.[26] Similarly, without reliable internet infrastructure, the use of Electronic Data Capture (EDC) systems and other eClinical tools becomes impractical, forcing studies to rely on slower, paper-based data management methods.[27]

To overcome these technological barriers, global Contract Research Organizations (CROs) are encouraged to implement cohesive clinical trial management systems when operating in emerging markets.[27] One effective strategies involves equipping technological devices with offline data entry capabilities, allowing data collection and storage even in the absence of an internet connection.[27]

## CONCLUSION

The globalization of clinical research is propelled by the pursuit of not only broader access to diverse patient populations but also by the hunt of cost effective, timely and accelerated regulatory approvals. While this shift offers significant scientific and commercial advantages to the clinical research enterprise system, it also brings on a myriad of critical challenges related to ethical oversight, regulatory harmonization, and infrastructural capacity in these settings. However, if the aforementioned challenges are addressed appropriately then the globalization of clinical research trials may hold an extensive potential for accelerated development of advanced medical therapies that could contribute meaningfully to tackling the global health needs.

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