OPINION EDITORIAL

Challenges in Conducting International Clinical Research in Low- and Middle-income Countries

Hailey Pineda, McMaster University

ABSTRACT

The most impactful research comes from the international collaboration of researchers from interdisciplinary backgrounds. The involvement of different countries, cultures, and perspectives is needed to combat the increasingly complex healthcare issues arising today. Although it is well accepted that this collaboration is key to meaningful research, many developing countries are often underrepresented within the literature. Research from low and low-middle income countries (LMICs) is needed, but there are many challenges that come with their inclusion. These differ between country and type of trial but are generally categorized into technological, cultural and geographical, financial, political and economic, human resource and infrastructure, and operational barriers [3-4, 9-14, 16-19]. Further exploration into these challenges, specific areas of need, and potential improvements are necessary for the future of clinical research and health outcomes of the global population.

SEARCH STRATEGY

The search strategy for this literature review was aimed at identifying studies discussing the benefit of international collaboration in research, disparities in clinical research by country income, and the challenges faced when conducting research. The studies used in this review ranged from 2008 to 2021. There were no restrictions placed on the date of publication.

A search using keywords and index terms was undertaken across the databases PubMed, BIOSIS Previews, Web of Science, and Google Scholar. Both the WHO International Clinical Trials Registry Platform and ClinicalTrials.gov were searched for clinical trials occurring specifically in LMICs. Lastly, the references list of all relevant articles were searched for additional studies. For example, the PubMed search was: ((Barriers OR Challenges) AND Conducting (Clinical Research OR Clinical Trials) AND (LMICs OR Low-middle income countries OR Developing countries)). Results from all searches were used to form the thematic barriers in Table I.

INTERNATIONAL CLINICAL RESEARCH

Global collaboration has been deemed as an indicator of high-quality research [1]. International collaboration within healthcare specifically allows for greater potential for discoveries of new treatments and therapies, as well as improving current ones. The integration of multidisciplinary approaches amongst skilled researchers is needed to combat the increasingly complex healthcare issues arising today. Global collaboration is extremely beneficial as it allows for the timely completion of clinical trials, the increased generalizability of results, and the inclusion of more perspectives and cultures [1]. Having multiple study sites around the world results in a more diverse sample, where more ethnic and cultural differences can be explored. The inclusion of heterogeneous populations aids in ensuring the results are more widely applicable to different people or groups [2].

This generalizability helps to maximize study outcomes. Collaboration also creates a foundation for education and mentorship among researchers [1]. The opportunity to collaborate allows researchers to share their knowledge, experience, and research methods with one another. Research procedures and standards of care vary throughout countries [3], so this dissemination of knowledge across continental divides can be beneficial in considering all perspectives. The networking and relationships made throughout the research process may even help strengthen the researcher's individual incentives and passion for conducting such research.

CLINICAL RESEARCH DISPARITIES BY COUNTRY INCOME

Despite the increases in international clinical research collaboration, there are still barriers to overcome. LMICs are resource-constrained and disease burdened countries; however, they are often underrepresented in research [4]. Data from the WHO International Clinical Trials Registry Platform indicates there was a total of 55, 062 registered trials in 2019, but only 14% of these occurred in LMICs (Figure 1) [5]. A 2018 study examined the registration of clinical trials over a seven-year period. Researchers found that only 5% of the registered trials occurred in low-income or low-middle-income countries [6]. Another study [7], also conducted in 2018, confirmed these same trends. The researchers only included oncology-related clinical trials within this study, but they still found that HICs comprised 71% of the total trials included, while LMICs only comprised 29% [7]. It is very evident that clinical trial rates remain concentrated in high-income countries (HICs), while LMICs are often less involved.

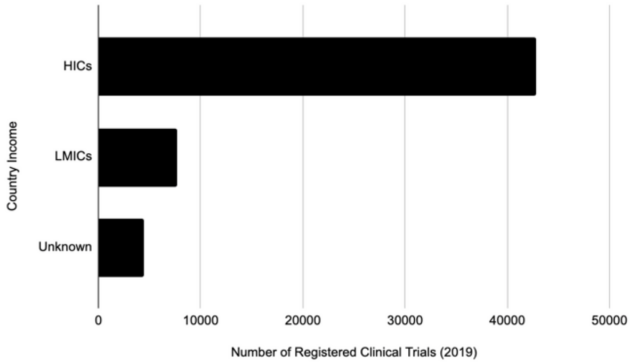

Figure 1. The number of clinical trials registered in 2019 by country income.
Data was obtained from the WHO International Clinical Trials Registry Platform (n=55, 062). Countries are broken down by income (high, low-middle, and unknown). HICs had the most registered clinical trials at 77.8% (n=42, 846) while LMICs had only 14.1% (n=7, 743).

COMMON CHALLENGES IN CONDUCTING INTERNATIONAL CLINICAL RESEARCH

With any clinical trial, there are challenges and barriers to be overcome. The challenges faced while researching in LMICs, are not as well understood as the more common Western research challenges. Less developed countries are often ridden with political instability, fragile health care systems, poverty, food, and disease crises [4, 8]. Sociocultural differences additionally impact the research process. Multiple systematic reviews have broadly categorized the major challenges faced when conducting such research. These include technological, cultural and geographical, financial, political and economic, human resource and infrastructure, and operational barriers [3-4, 9-14, 16-19] (Table I). It is important to also consider that these barriers will additionally differ between country and type of clinical trial. Language barriers are routinely identified as one of the most challenging to overcome in clinical research [3, 9]. Specifically, translating informed consent forms (ICFs) poses a major threat in miscommunicating vital information to the patient, but also for maintaining data accuracy [9]. Financial barriers are often also deemed one of the more challenging [4, 9, 10, 11].

Most often, it was reported that there was simply a lack of funding to carry out the study goals. The variation in the type of trial can additionally cause a variation in the payment plans/methods used [9]. This can make it difficult for a research team to access the study funding [9]. It is worth noting that language barriers can interact with financial barriers when translating contracts and dealing with fluctuating currency exchange rates [9]. Lack of trained research personnel was found to be another notable challenge. Highly skilled researchers are necessary to carry out quality studies; however, many countries lack the proper training programs and certifications to make this possible [12]. In India, for example, researchers found that fewer than 200 of their physicians have been trained in Good Clinical Practice (GCP) [4]. Lastly, issues surrounding patient enrollment, willingness, and trust are frequently seen as major challenges. A survey given to various principal investigators (PIs) found that 44% of them ranked patient enrollment as the greatest difficulty when conducting research [13]. Patient and community distrust in research is also a growing concern, especially when involving LMICs. For many non-expert audiences, the term 'research' can lead to ideas of unethical experimentation or being perceived as 'guinea pigs' [14]. The long history of ethical breaches in clinical trials conducted in LMICs makes hesitancy more than just misperception. For example, many treatments and procedures are widely unavailable or unaffordable throughout LMICs. As a result, many people may feel that their participation in research is the only way to receive treatment [15]. This gravely compromises the values of GCP and informed consent conduct – both of which are essential for strong and ethical clinical trials.

It is important to note that this lack of trust can often stem from cultural differences or from deeper socioeconomic issues as well. For these reasons, there can be a weakened desire to participate in a trial or distrust developing throughout the trial's process for participants in LMICs.

Table I. Common challenges in conducting international clinical research

Thematic Challenges	Sub-themes
Technological	Unstable internet connectivity [12]
	Inadequate access to reliable technology [12]
	Less comfort and/or experience with data collection [12]
Cultural and Geographical	Language barriers between participants and/or the research team [3, 9]
	Difference in time-zones [11]
	Patient or community distrust of research teams [14]
	Lack of importance placed on conducting research [17]
	Few incentives for participating in research [17]
Financial	Study funding was insufficient [4, 9, 10, 11]
	Difficult accessing the study fund [9]
Political and Economical	Political instability or regression [18]
	Environmental distress [18]
	Burden of other communicable and non-communicable diseases and/or epidemics [19]
Human Resource and Infrastructure	Understaffed hospital sites [4]
	Under-resourced sites [4, 11]
	Poor infrastructure of the country and/or hospital site [12]
	Insufficient training of research personnel [4, 10, 11]
	High turnover rate or migration of research personnel [12, 16]
	Lack of commitment from the research team [4]
Operational	Difficulty recruiting patients [4, 11, 13]
	Unsupportive administrative staff [9]

CONCLUSION

The imbalance between research occurring in HICs and LMICs creates an unmet need, and consequent responsibility, for conducting relevant research in these environments. Although there has been an increase in the amount of global collaboration occurring, it is crucial that LMICs are given the opportunity to participate and contribute. The difference between LMICs and the more developed world creates a wide array of unique problems that need to be addressed. There is an extensive summary of common challenges when carrying out clinical research within the literature; however, there is a lack of comparison between countries experiencing the same issues. Connections must be made between countries so that solutions can be implemented. Improving the process in which clinical trials are currently conducted ensures more accurate data collection and results, widespread solutions, and ultimately, the improved health outcomes of the global population.

REFERENCES

1. Marshall, J. C. (2017). Global collaboration in acute care clinical research: opportunities, challenges, and needs. Critical care medicine, 45(2), 311-320.

2. Lang, T., & Siribaddana, S. (2012). Clinical trials have gone global: is this a good thing?. PLoS medicine, 9(6), e1001228.

3. Bansal, N. (2012). The opportunities and challenges in conducting clinical trials globally. Clinical Research and Regulatory Affairs, 29(1), 9-14.

4. Alemayehu, C., Mitchell, G., & Nikles, J. (2018). Barriers for conducting clinical trials in developing countries-a systematic review. International journal for equity in health, 17(1), 1-11.

5. World Health Organization (WHO). (2020). Number of clinical trials by year, country, WHO region, and income group (1999-2019).

6. Drain, P. K., Parker, R. A., Robine, M., & Holmes, K. K. (2018). Global migration of clinical research during the era of trial registration. PLoS One, 13(2), e0192413.

7. Ramaswami, R., Paulino, E., Barrichello, A., Nogueira-Rodrigues, A., Bukowski, A., St. Louis, J., & Goss, P. E. (2018). Disparities in breast, lung, and cervical cancer trials worldwide. Journal of global oncology, 4, 1-11.

8. Imam, A., Wariri, O., Dibbasey, T., Camara, A., Mendy, A., Sanyang, A. N., ... & Idoko, O. T. (2021). Conducting clinical research in a resource-constrained setting: lessons from a longitudinal cohort study in The Gambia. BMJ global health, 6(8), e006419.

9. Minisman, G., Bhanushali, M., Conwit, R., Wolfe, G. I., Aban, I., Kaminski, H. J., & Cutter, G. (2012). Implementing clinical trials on an international platform: challenges and perspectives. Journal of the neurological sciences, 313(1-2), 1-6.

10. Khoja, A., Kazim, F., & Ali, N. A. (2019). Barriers to Conducting Clinical Trials in Developing Countries. The Ochsner Journal, 19(4), 294.

11. Seruga, B., Sadikov, A., Cazap, E. L., Delgado, L. B., Digumarti, R., Leighl, N. B., ... & Cufer, T. (2014). Barriers and challenges to global clinical cancer research. The oncologist, 19(1), 61.

12. Aluisio, A. R., Waheed, S., Cameron, P., Hess, J., Jacob, S. T., Kissoon, N., ... & Razzak, J. (2019). Clinical emergency care research in low-income and middle-income countries: opportunities and challenges. BMJ global health, 4(Suppl 6), e001289.

13. Cullati, S., Courvoisier, D. S., Gayet-Ageron, A., Haller, G., Irion, O., Agoritsas, T., ... & Perneger, T. V. (2016). Patient enrollment and logistical problems top the list of difficulties in clinical research: a cross-sectional survey. BMC medical research methodology, 16(1), 1-9.

14. Scharff, D. P., Mathews, K. J., Jackson, P., Hoffsuemmer, J., Martin, E., & Edwards, D. (2010). More than Tuskegee: understanding mistrust about research participation. Journal of health care for the poor and underserved, 21(3), 879.

15. Gyawali B, Carson LM, Berry S, Moraes FY. Challenges of globalization of cancer drug trials- recruitment in LMICs, approval in HICs. The Lancet Regional Health - Americas. 2022 Mar;7:100157.

16. Duvivier, R. J., Burch, V. C., & Boulet, J. R. (2017). A comparison of physician emigration from Africa to the United States of America between 2005 and 2015. Human resources for health, 15(1), 1-12.

17. Research capacity strengthening in LMICs: A Rapid Evidence Assessment. (2019). Available from https://assets.publishing.service.gov.uk/media/5d42be4eed915d09d8945db9/SRIA_-_REA_final__Dec_2019_Heart___003_.pdf

18. Acharya, K. P., & Pathak, S. (2019). Applied research in low-income countries: why and how?. Frontiers in Research Metrics and Analytics, 4, 3.

19. Perel, P., Miranda, J. J., Ortiz, Z., & Casas, J. P. (2008). Relation between the global burden of disease and randomized clinical trials conducted in Latin America published in the five leading medical journals. PloS one, 3(2), e1696.