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CHALLENGES AND ETHICAL CONCERNS IN CONDUCTING CLINICAL TRIALS IN LOW AND MID-INCOME COUNTRIES: AN OVERVIEW

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ABSTRACT

Clinical trials are vital in drug improvement and worldwide to assess varied populations. Today, scientific trials are massive and tightly regulated. Pharmaceutical organisations have to comply with moral requirements while keeping excessive epistemic standards. The lower and middle-income communities (LMIC) countries may be a lucrative destinations for clinical trials. People dwelling in such impoverished communities have limited healthcare support and economic constraints, thus inclining them to participate in the dangerous clinical practice compared to people from developed countries. Therefore, the ethical concern of proper awareness and benefits may be compromised. They may not ask or claim the benefits of participating in the clinical trial in situations of side effects or unforeseen outcomes that debilitate their health or well-being. While the centre of attention is on the moral or ethical medical trial implementation during the research development phase, there has to be an emphasis on monitoring the concern and welfare of the participants throughout the study. This article provides insights on several challenges and problems in conducting a clinical trial in LMIC and necessitating the essential monitoring obligations to make the trails safe and in the overall interest of humanity. Challenges beyond patient participation, monitoring, overlapping responsibilities, and lack of standards and safety measures. This article also tries to make an honest attempt to oversee some of these serious issues, challenges and ethical concerns in patients participating in the clinical trials from LMIC.

KEYWORDS: COVID-19, LMIC, clinical trials.

INTRODUCTION

Covid-19 has undoubtedly disrupted the healthcare systems worldwide. There is a severe impact on healthcare infrastructure internationally. The developed and underdeveloped nations' healthcare systems are seriously hampered due to COVID-19. Increased morbidity and mortality are associated with COVID- 19, resulting in a burden on the health system and the economy.[1,2] The overall health system and functioning affect and impact the patients and the healthcare providers. For example, patient emergency visits have significantly decreased during the COVID 19 pandemic [3]. In addition, various vaccination campaigns have been halted due to the emergence of COVID-19 [4], which may contribute to oblique morbidity and mortality.

The highest impact on the healthcare system was seen in the developing and underdeveloped countries where healthcare delivery systems are still naive. Covid-19 has also impacted and limited the execution of scientific trials in resource-limited populations. As countries underwent lockdowns to curtail the ever-increasing Covid-19 pandemic, the loopholes in the healthcare systems became more prominent. The clinical trials took a significant setback. The unprecedented pandemic highlighted the lack of infrastructure, heterogeneity of aid availability amongst countries, unfamiliarity with the changing medical trial regulations, cultural/ethical issues, and constraints around data-sharing. The large-scale trials affected during the pandemic were performed in LMICs for HIV/AIDS-associated malignancies and cervical cancers.[5,6,7]

Keen interest has been shown by pharmaceutical companies in conducting clinical trials globally and has moved inexorably toward low- and middle-income nations (LMIC). This style has raised a range of concerns, including whether the lookup being carried out is of cost to public fitness in these nations or whether economically deprived populations are being exploited for the advantage of sufferers in wealthy countries. Nevertheless, scientific trials and healthcare care that accompany them can immediately gain patients, precisely those who would in any other case have no, or solely a little, chance to get medical care services. Consequently, it is fine-tuned stability between the pharmaceutical groups and participant patients from the LMIC to ensure that all aspects benefit.[8]

Declaration of Helsinki was revised by the World Medical Association, an announcement of standards for the ethical habits of clinical research, in October 2000. The National Bioethics Advisory Commission (NBAC) issued a file on moral and coverage troubles in worldwide research earlier this year. The AMA handed a piece of new advice on moral ethics in worldwide research at its 2001 Annual Meeting in June. The Council for International Organizations of Medical Sciences is presently revising its 1993 suggestions for the ethical behaviour of lookup involving human subjects. [9] This article identifies the challenges and ethical concerns in conducting clinical trials in lower and mid-income countries.

Main Content

The records of medical trials and their subsequent globalisation can be traced back to the thalidomide scandal in Germany in the early 1960s. Many newborns had severe deformations of their extremities; it is subtly clear that thalidomide, a sedative developed, triggered delivery defects in infants whose moms took the drug during pregnancy. Public outrage over the devastating results of the drug and the truth that it had not been sufficiently examined for drug safety fuelled dialogue inside the US Foods and Drug Administration (FDA). It shortly led to regulation to enhance the drug safety testing of new drugs. The so-called Kefauver- Harris Amendments have been exceeded to forestall any other thalidomide catastrophe and—although not immediately associated with the drug scandal — added the requirement for drug manufacturers to show drug effectiveness besides safety.[10]

Multicenter research is regularly reviewed by IRBs, an expensive but redundant procedure which ensures the safety of patients involved in trials. Scientific trials went overseas in the 1980s, considering the stringent FDA guidelines. FDA rules are now not the sole purpose of many clinical trials moving to LMIC. Consequently, recruiting different patient populations is an essential parameter in checking the safety and efficacy of drugs in different population samples and ethnic groups. However, it stays a critical bottleneck in clinical research. The organisations have become less immune to behaviour trials because it is less challenging to discover participants in the LMIC.[11] Researchers started exploring the Scandinavian, the UK, Eastern Europe, Indian, and China foreign sites. It is estimated that the 20 biggest US pharma companies have conducted their Clinical trials outside the USA.[12]

Moreover, the COVID-19 pandemic has dramatically impacted scientific trials in high-income international locations. The main impact on clinical trials was trail closures, stay-at-home orders, logistic chain issues, and participant reluctance to visit clinicians' workplaces and hospitals, among other barriers.[13] Many of these difficulties have been exacerbated in the LMICs. Other challenges stated as an outcome of the pandemic include interactions with sponsors and CROs about enhancing trial procedures and protocol changes and deviations −either intentional or unintentional− with unknown results, questioning the scientific integrity, interpretation, and conclusions.[14] In addition, the warning has been given by few authors about the opportunity that pressured modifications delivered in medical trials by using the pandemic −such as reduced follow-up visits, participants' poorer intellectual or bodily health, or even contamination with the novel coronavirus− may additionally intrude with the consequences of the treatment's dangers and advantages.[15] Besides, the influence of COVID-19 on medical trials is unevenly relying on the therapeutic area. One document located declines in participant enrolment ranging from 34% for respiratory ailments up to 80% for endocrine diseases, with intermediate percentages for different therapeutic areas (47% for infectious diseases, 48% for oncology, 64% for dermatology, 68% for neurological illnesses, and 70% for cardiovascular diseases.[16]

As significant barriers have been recognised in conducting trials that lead to mobility and tour restrictions, lack of sufficient applied sciences, and disruptions in logistic chains, COVID-19 has led us to 'rethink' how scientific trials are conducted. Some options proposed to overcome these challenges [17, 18] encompass transferring scientific websites to nations and areas much less impacted by COVID-19, virtualisation of various factors of the trial (such as far off consent, far-flung randomisation, and far off information seize and reporting), use of science to carefully screen affected person extent and drug furnish to reduce disruptions, to introduce artificial manipulate fingers from historic trial records blended with synthetic talent algorithms, or imparting in-home medical services. In particular, scientific innovation can grant new equipment to ensure scientific research continuity and success throughout the pandemics. An instance of this innovation is a risk-based predictive analytical method powered using desktop mastering that can provide predictions and forecasts to assist decision-making throughout scientific operations administration [19]

The essential ethical troubles surrounding RCTs have been with the ethics of scientific trials. Participation in a medical trial entails an extended threat to regular medical care, mainly due to the conceivable publicity of unexpected results of a new treatment. These dangers are genuinely not offset via a potential scientific benefit because the fundamental give up of the trial is now not that of treating trial members; however, as a substitute, producing generalisation in a position of scientific knowledge. Moral anxiety has countless facets; the following thing of the RCT is spotlighting growing challenges in the ethical, informed consent, use of placebo, randomisation, and safety of participants. [20]

It cannot be denied that pharmaceutical businesses take their lookup protocols to the low and middle-income

countries, considering the financial factor and human resources, as the cheap labour in middle-earning international locations such as Africa, China, and India is markedly more valuable than in high-income countries. In addition, the regulatory burden related to the behaviour of medical lookup in high-income settings, like the United States and the European Union, will increase the burden of financial outflow further. The medical enterprises seek exceptional financial gains with profit maximisation by conducting research trials in the LMIC.[21,22]

Furthermore, as various diseases and ailments are taking a severe toll on LMIC, it is unclear when new treatment drugs will be less expensive in these countries. The clinical trials in LMIC help the government and community tackle serious infections, especially when the health system resources are limited and the medications are expensive. For example, Hepatitis C, an infectious disease that can lead to liver cirrhosis, is on the upward trend globally. Growing international locations elevate the absolute best burden with infection quotes as excessive as 11% in Egypt, 4.8% in Pakistan and 3.2% in China. During the previous decade, lookup has improved a new medication that works extra effectively, takes less time and with fewer side effects. In distinction to the prior remedy regimens, these all-oral medicines no longer require regular interferon injections, making them perfect for faraway settings. The drugs are simply marketing, with more in the pipeline. However, their higher cost makes them unaffordable for citizens from the LMIC. Similarly, as with AIDS medication, it will take a long time till they are accessible to most LMICs.[11]

Though not all clinical trials conducted in LMIC have a grey lining, various trials have raised ethical concerns about clinical trials. In the PolyIran trial, the illiteracy of the participants necessitated the use of verbal consent and documented by the hospital staff. However, troubles such as when verbal consent is ideal and what practices should be in the vicinity to ensure correct verbal exchange of learning about records and voluntary consent to find out about participation are questionable.[22, 23] In the PASTAL trial, pregnant ladies supplied written permission for participation. However, their male companions did not. Criteria for a waiver of consent (socially precious research, minimal risk, and infeasibility with support) require considerable interpretation. How ought minimal chance be understood (e.g., is the opportunity of accomplice violence regular with minimal risk), and when is a learn about 'in-workable' if consent is required (e.g., decrease recruitment, extra lookup group of workers needed, cost); all these require due consideration if they are to be applied reasonably and consistently. Thus, the PolyIran trial raises the concern of how widely post-trial admission should receive the medication — or to the trial members solely or all those who contributed statistically to the analysis? The PASTAL trial highlights the concern of making the intervention medication available even after the trial. There is an urgent want for ethics schooling and potential construction related to CRTs in LMIC settings to avoid exploitation.[22,23]

CONCLUSION

The involvement of the clinical trials in LMIC is the need of the hour, especially for diseases prevalent in the population, and will provide an economic benefit in terms of affordable medications. Sometimes these provide the underprivileged people with the only hope of receiving the medication. Thus, every CT needs to be thoroughly planned, evaluated, regulated and ethically correct before involving the people from the LMIC.

An ethical, scientific lookup enhances the proof base (knowledge) to deliver more significant advantages to human populations towards the clinical trial, regardless of their improvement status. The growing presence of medical trials in developing nations displays the quintessential truth that such international locations signify areas of interest for pharmaceutical corporations and medical organisations. It additionally shows the requirement for developing assurance in the country's health infrastructure to reliably operate and comply with the necessities of the International Conference on Harmonisation-Good Clinical Practice (ICH-GCP). As the ethics of scientific trials become more complicated as scientific research progresses, various factors will be required to be taken care of, following the ICH-GCP guidelines. Similarly, community awareness about clinical trial regulations, national and international policies, and community awareness should be practised to gain their confidence and contribute to overcoming clinical trial challenges, especially in low and middle-income countries.

Conflict of Interest

There is no conflict of interest.

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Data collection and writing by Dr Pankaj Mandale

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