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Jenei, Kristina, Moraes, Fabio Y. and Gyawali, Bishal (2023) Globalisation of clinical trials in oncology: a double-edged sword? BMJ Oncology, 2 (1). ISSN 2752-7948

https://doi.org/10.1136/bmjonc-2023-000163

BMJ Oncology

Globalisation of clinical trials in oncology: a double-edged sword?

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To cite: Jenei K, Moraes FY, Gyawali B. Globalisation of clinical trials in oncology: a double-edged sword? *BMJ Oncology* 2023;**2**:e000163. doi:10.1136/bmjonc-2023-000163

Linked

► http://dx.doi.org/10.1136/bmjonc-2023-000101

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In this issue of *BMJ Oncology*, Payedimarri *et al* provide insights into the global distribution of industry sponsored clinical trials for breast, lung and colon cancer.[1] Of the 4177 trials conducted up until June 2018, most (77.9%) clinical trials were conducted in high-income countries (HICs), while the rest occurred in middle-income settings. There were no clinical trials that included sites in low-income countries (LICs). Concerningly, of the 1854 clinical trials that had completed in 2018, more than half (63.4%) had not shared their results 4years later.

Over the past few decades, there has been an increase in the globalisation of clinical trials—the practice of HICs enrolling patients from low-income and middle-income countries (LMICs). Involving participants and investigators from LMICs in clinical trials has been generally welcomed given the potential for increased collaboration, improved access to novel medicines and better-quality data to improve treatment decisions in LMICs. However, Global North-South collaborative trials have also raised serious ethical concerns given the power held by the pharmaceutical industry in running drug trials, vulnerabilities of patients and clinicians in low-resourced countries, and lack of access to interventions after the trials complete, especially within public health systems. Previously, Wells *et al* studied a similar cohort of clinical trials and showed that the use of surrogate endpoints was more common in breast cancer trials, lung cancer trials were more likely to show substantial benefit, and gastrointestinal cancer trials were more likely to be published in a lower impact factor journal.[2] Payedimarri *et al* add to this literature by describing the geographicl distribution of industry-sponsored oncology trials and whether these studies meet their ethical obligation to publicly report results. Their findings have important considerations.

First, the authors found a complete absence of sites from LICs. This is consistent with the finding from Wells *et al* who reported only 9% of GI cancer trials from LMICs.[2] Most clinical trials were conducted exclusively in HICs which highlights the disparities between HICs and LMICs with regards to access to clinical trials and the lack of high-quality data for clinical decision making for patients in LICs. Unfortunately, a lack of infrastructure and robust healthcare systems in LMICs perpetuates these disparities as drug developers are less likely to conduct studies in locations that cannot administer health interventions as intended (however, this does not stop manufacturers from selling the product within these countries after the drug comes to market). Collaboration between high-resource and low-resource settings would bring substantial advances to the field of oncology, improve capacity in low-resourced settings through infrastructure and peer mentorship, and ultimately improve health outcomes for those that experience the highest burden of disease. However, the pharmaceutical industry is guided by financial incentives that are often not aligned with global health and this reciprocity seldom occurs.

Second, the authors found that the geographical distribution of clinical trials changes when stratified by study phase. Early phase clinical trials were more likely to be conducted in HICs, whereas phase III studies were more likely to be conducted in Middle-income countries (MICs). Again, this can be explained via incentives. Since phase III trials require larger sample size, running such trials outside of HICs will help in faster accrual. Indeed, poor accrual is the most common cause for clinical trials to fail[3] and studies claim 3–7 times faster accrual in MICs versus that in Western Europe and North America.[4] In addition, the cost per participant is cheaper in MICs compared with HICs. This explains why more phase III cancer drug trials are now being conducted in MICs- China and Russia were the the most common UMICs and Ukraine and India were the comments MICs in the current study.

However, faster accrual is probably not the only incentive for industry to go global for running phase III RCTs. There have been concerns that these trials are conducted outside of HICs because the trial employed a control

arm that was beneath the standard of care in HICs and would not have received the ethical approval in HICs. In addition, postprotocol therapy would also not resemble what patients in HICs would have received. This creates a bias favouring the experimental agent, and thus provides incentives for the industry to run trials in settings where an inferior control arm would be regarded acceptable and access to standard post-protocol therapies would remain poor.[5] Although there can be an argument that such trials help access to new drugs for patients in MICs, regrettably, data show otherwise. Among the trials that led to approval of drugs by the Food and Drug Administration, only 9% of MICs had access to these drugs 5 years postapproval despite these countries having participated in those trials (compared with 46% of HICs).[6]

Third, it remains unclear what proportion of these industry-sponsored trials were from local industry or multinational companies. Furthermore, we do not know whether the drugs tested in these trials are available or approved in the participating countries. Exploitation occurs when patients from LMICs do not benefit from the knowledge nor treatments produced from these studies.[7] Previous research has found that oncology trials do not match the global burden of cancer disease,[8] nor does the research output sufficiently include investigators from LMICs,[9] therefore, there may be reason to believe that the majority are companies from HICs and not local industry. An important area for future research would be to characterise the demographics of the study sponsors and continuity of treatment after clinical trials complete, such as investigating whether tested interventions remain accessible in LMICs or whether health system capacity improves—two criteria defined as 'fair benefits' for those that participate.[10]

Fourth, there is non-transparency in the reporting of the results and participating countries. The authors found 63.4% of clinical trials had not entered their results in ClinicalTrials.gov by the time of their updated analysis 4years later. Furthermore, only 236 (12.7%) of the 1854 completed trials had posted their results within the 12-month time frame required by international organisations such as the WHO. Investigators have an ethical duty to share results in a timely manner as non-transparency complicates clinical and regulatory decision-making and can expose future participants to harm given a lack of demographic data. Reporting requirements are outlined by several other organisations such as the International Committee of Medical Journal Editors and the World Medical Association Declaration of Helsinki. Furthermore, legislation has been introduced in Europe and the USA that mandate clinical trial results be posted to public registries.[11] However, the authors reveal that reporting is sparse and enforcement is likely weak which underscores a major gap in the regulatory system.

Despite substantial advances in oncology, serious inequities remain between HIC and LICs. Payedimarri *et al* demonstrate that the clinical trials are no exception to this gap given the lack of involvement in LICs. While the globalisation of oncology trials offers many benefits to the field, it can also be a double-edged sword if enforcement and oversight is not in place to ensure those that risk their health also benefit from the research outcomes. When advocating for more clinical trials in LMICs, we should ensure that we are advocating more for locally tailored, investigator initiated, pragmatic trials that address local needs and access rather than the parachutic and parasitic clinical trials that only use patients from LMICs to get drugs approved back in HICs.

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Contributors KJ: manuscript writing. FM: manuscript editing. BG: manuscript writing, editing and supervision.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests KJ reports no conflicts. FM reports receiving honoraria from Astra Zeneca and Eletka ltda. BG reports receiving consulting fees from Vivio Health.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Commissioned; internally peer reviewed.

Data availability statement No data are available.

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