Challenges of globalization of cancer drug trials-recruitment in LMICs, approval in HICs

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An increasing number of cancer clinical trials are conducted in low-and-middle-income countries (LMICs).[1] Increasing the representation of LMICs in cancer drug trials is encouraging, but we are concerned about research parasitism and parachutism in these practices.[2] In this commentary, we explore how LMICs may not have been served by participating in these global cancer drug trials.

Despite reduced complexity and lower cost being commonly cited reasons for the industry's motivation in running cancer drug trials in LMICs,[1] there is another incentive that is less frequently discussed — the possibility of running a trial with a substandard control arm that would not be considered appropriate in a high-income country (HIC). For example, a new immune checkpoint inhibitor (ICI) (cemiplimab-rwlc) for patients with advanced Non-Small Cell Lung Cancer Treatment (NSCLC) with tumor PD-L1 expression of 50% or more was run as an international trial (EMPOWER-Lung 1) in several HICs (such as Australia and Spain) and LMICs (including Brazil, Chile, Colombia and Mexico), not including the USA. The trial compared cemiplimab against chemotherapy control between June 2017 and February 2020.[3] This was done despite pembrolizumab, another ICI, having been established as the standard of care for this patient population after demonstrating improved survival versus chemotherapy in a randomized controlled trial.[4] Nevertheless, the EMPOWER-Lung 1 trial enrolled patients to a trial with chemotherapy as the control arm and proved, unsurprisingly, the superiority of immunotherapy, leading to the drug's approval by the US FDA.[5] This practice of running substandard trials in LMICs to get a drug approved in HICs is unacceptable for several reasons.

Firstly, the Helsinki Declaration states that control arms in randomized controlled trials (RCTs) should receive the "best-proven intervention",[6] not the standard of care in the local research setting. Investigators from HICs — the majority of which are sponsored by the pharmaceutical industry — frequently conduct clinical cancer trials in LMICs, where an inferior control arm is used under the guise of local inaccessibility to the global standard of care.[1] This enables studies that would not meet ethical standards nor be able to recruit participants in HICs to be run in LMICs. The described practice allows "me too" drugs to gain approval for use in HICs without conducting a proper rigorous clinical trial against a standard comparator.[7] This perpetuates an exploitative form of cancer research that enables unethical trials to be run in LMICs. Instead of improving equity, this discriminatory practice exacerbates inequity in global cancer care.

Another major flaw of research parachutism is that it rarely benefits the people of the countries where the drugs are tested. A cross-sectional analysis of trials seeking FDA approval for cancer drugs found that 0% of LMICs contributing research participants received access to the drug within 1 year of FDA approval, in contrast to 13% of HICs.[8] It could be argued that People with cancer from LMICs are being exploited by participating in trials that will only reap benefits for people in HIC.

Thirdly, these studies capitalize on the inaccessibility of treatment in LMICs to garner participation. Access to modern cancer treatments is often a significant challenge in LMICs.[9] By conducting research in countries where these treatments are largely unaffordable, investigators from HICs put patients in a situation in which they may feel participation in the trial is their only way to access treatment.[1] These circumstances can severely compromise the voluntary nature of consent required for the ethical conduct of a trial.[6]

Finally, conducting trials in LMICs to get drugs approved in HICs without serving patients in the local community hijacks the local research priorities and agenda. Focusing on these types of trials for LMICs will lead to lost opportunities for patients to participate in more valuable, accessible clinical trials that are more relevant to the local community and a better use of scarce research resources.

The advances and innovations in clinical cancer research offer significant potential for global benefit. To balance the previous points, it is important to acknowledge that the increased availability of cancer medicines in the form of "me too" drugs may increase access to cancer control for many regions and individuals by offering more competitive and affordable prices of drugs. However, me-too drugs leading to potential competition, reduced prices and improved access is a theoretical construct that hasn't yet been proven in global

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oncology. Nevertheless, if such trial were to be done, the ethical design would be a non-inferiority design against the established global standard of care.

We urge the global cancer community, research ethics boards and regulatory bodies to reject clinical trials that employ inferior control arms. The proliferation of such exploitative research will foster continued inequities in global cancer care while promoting unethical trials that take advantage of strained health systems in low-resource settings. New cancer drug trials should not only be held to the highest standards of scientific and ethical scrutiny but should only be conducted if the results hold the potential to offer significant value to patients with cancer in the local region. This may require long term commitment from the manufacturer of the drug for continued access to the drug for the local patient population and early engagement of local health policy makers to ensure the treatment will be sustainable and affordable. Lastly, research funders should increase opportunities for cancer research led by investigators and patients in LMICs who are driving the agenda of what research questions have the greatest value for them. Increasing opportunities for research, funding, and publication for these investigators will help reduce the disparities that prevail in cancer research.

Contributors

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