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Brief Report

Phase 1 Clinical Trials: Challenges and Opportunities in Latin America

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Patients from Latin America are anticipated to face a massive cancer burden in the forthcoming years. Piñeros et al[1] predicted that cancer incidence in the Latin American and Caribbean regions will increase by 66%, reaching over 2.4 new cases by 2040. Despite the considerable advances in cancer prevention and screening programs, the accessibility of cancer treatment is a persistent challenge in vulnerable populations. This is particularly evident for patients harboring tumors with limited therapeutic options. The availability of expensive innovative treatments is even more limited, exacerbating their difficulties.[2] Also, Werutski et al[3] demonstrated that worse economic status (expressed as gross domestic product per capita) reflects cancer-related mortality for specific cancer types.

In May 2014, a phase 1 unit in the United States (US) enrolled its first patient to receiving the tyrosine kinase inhibitor, larotrectinib. After the first results showed an impressive benefit for patients with tumors harboring an NTRK fusion, larotrectinib obtained accelerated approval from the US Food and Drug Administration (FDA) in November 2018. Subsequently, the Brazilian regulatory agency (ANS) responsible for drug evaluation and commercialization granted approval for larotrectinib in July 2019. In May 2022, exactly 8 years after the first American citizen had the chance to receive a disruptive cancer treatment, ANS denied the approval of health insurance coverage for larotrectinib in Brazil. This timeline highlights that patients with tumors having limited treatment options in these regions could have benefitted from access to a promising drug had there been phase I clinical trials conducted in Brazil.

Chacón and colleagues[4] conducted a study published in the American Society of Clinical Oncology Connections examining clinical trials registered at ClinicalTrials.gov, showing that 81% of all ongoing clinical trials were from Europe or the US. The Latin American population is currently above 600 million people, with 1.3 million new cancer cases, according to the Latin American Cooperative Oncology Group 2021 annual report, but only 4% of clinical cancer trials are ongoing in the region. Additionally, as highlighted in the report, Latino (people from Latin America or descendants of people from Latin America) and Hispanic (people who speak Spanish or are descended from people who speak Spanish) populations are slowly increasing in clinical trials. However, their presence in the world's research production is still disproportionately low relative to geographic size and overall population.[5] Regarding the trial phase, Silva et al[6] identified a notable concentration of phase I clinical trials in regions such as the US (N = 170), Japan (N = 17), and Europe (N = 91), whereas Latin America was underrepresented with only a limited number of trials (N = 4). When phase 3 trials were evaluated, a more balanced distribution of trials across regions was observed.[6] Therefore, it is evident that those countries need and deserve phase 1 clinical trials.

Phase 1 trials have traditionally been conducted in developed countries. The lack of clinical infrastructure and scientific rigor in underdeveloped settings was believed to compromise patients' safety and trial results.[7] However, Kapiriri et al[8] dissected this issue and revealed increasing evidence of the capacity of many low- and middle-income countries to take a leading role in developing rigorous clinical trial programs. At this point, the next question would be: Why should the industry consider Latin America? Several key factors influence a country's competitiveness in receiving clinical drug trials. These include patient recruitment capability (access to patients and investigators' motivation and commitment), cost (site contracts and sponsor-site

collaboration), infrastructure (site resources and experience), and ethical and regulatory policies.[9] Although these factors are well studied for late-phase trials, the general assumptions can be transposed to phase 1 research.

The extensive accessibility of FDA-approved targeted treatments in the US, potentially deterring patient participation in clinical trials, does not find an analogous reflection in resource-limited countries. Mosegui and Villar[10] evaluated the regulatory approvals of biological cancer drugs registered in the regulatory agencies from Brazil, Colombia, Mexico, the US, and Spain from 2014 to 2019. Overall, the US had the highest number of first registrations. Approvals in Spain, Brazil, Colombia, and Mexico occurred 900, 1914, 595, and 2776 days (median) after the US approvals, respectively.[10] This metric demonstrates how early-phase trials can provide opportunities for accessing cancer drugs in Latin America.

Moreover, Latin America not only has an enormous number of patients but also brings an ethnic diversity desirable in clinical research. According to Turner et al,[11] only 43% of the US-based trials conducted from 2000 to 2020 reported ethnicity data. Among those who reported race or ethnicity, most participants were White (median 79.7%). Latinos were significantly underrepresented, with a median enrollment rate of 6.0% versus a census population of 16.3%.[11]

Regarding the regulatory domain, Ndebele et al[12] described the challenges associated with conducting clinical trials in resource-limited settings. Investigators involved in multicountry clinical trials must be aware of the regulatory environment in each collaborating country. Also, material and data transfer agreements may be complex. The ethics committee evaluation processes may delay the efficient implementation of clinical trials, thereby postponing patients' access to potentially life-changing medications.[12] Moreover, primary investigators must guarantee continued study monitoring up to study completion to ensure data integrity.[13]

Gómez et al[14] surveyed medical oncologists from emerging countries to understand the insider's perception of conducting clinical research in their respective countries. The challenges identified appeared mainly in the education, regulatory, and financial domains. However, in Latin America, investigators have 7 years of overall experience, the ability to speak foreign languages, are highly motivated to participate in the trials, and have high-level training received abroad (US or Europe).[14] These characteristics, combined with low infrastructure, procedural, and labor costs compared with developed countries, create an attractive scenario for international industries.

Finally, it is important to address a sensitive issue closely related to research. Technology supplies, which are often lacking in resource-limited countries, can help mitigate clinical trial challenges, such as protocol design errors, slow recruitment, personnel training, and monitoring, as well as data management, analysis, and reporting.[15] This can be especially sensitive for phase I trials, accelerating the timeframe from the study implementation phase to database lock. Increasing funding in science, engineering, and mathematics is essential for improvement in quality research from Latin America.

In conclusion, although there have been notable advancements in cancer prevention and screening programs, the challenge of accessing adequate treatment persists in economically vulnerable countries. Despite its substantial population, the disproportionately low availability of early-phase clinical trials in Latin America underscores the urgent need for increased research efforts. Latin America's potential for patient recruitment and cost advantages make it an attractive region for industry consideration. Addressing challenges related to regulatory processes is crucial to enhancing clinical research and improving treatment accessibility in the region. In Brazil, pending legislation (PL 7082/2017) could represent an important improvement, warranting numerous good practice regulations for clinical research, including a maximum time to receive regulatory approval for a research protocol. This legislation is under consideration with the Senate and represents a hope for those treating cancer who support the development of clinical research and better access to new drugs.

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