

Personalizing Precision Oncology Clinical Trials in Latin America: An Expert Panel on Challenges and Opportunities

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ABSTRACT

The participation of patients in precision oncology trials needs to fulfill molecular-based selection criteria. This strongly limits accrual, and as a consequence, screening successes have decreased, costs have increased, and fewer subjects are enrolled. To achieve narrowed targets, studies have been forced to be multicenter and multinational to reach a larger pool of candidates. However, this globalization faces many challenges, as, for example, in the case of precision oncology trials. These trials have a complex structure that is dependent upon a high-tech

infrastructure and knowledge in a dynamic environment. Given the movement of precision clinical cancer research to regions other than Europe and the U.S., it is important to evaluate the feasibility of performing such trials in lower-middle- and low-income countries. Here we critically discuss the advantages of conducting precision oncology clinical trials in Latin America and make suggestions on how to overcome the main challenges involved. **The Oncologist** 2019;24:e709–e719

Implications for Practice: Precision clinical trials in oncology are studies that require candidates to have tumors with specific molecular alterations, which are considered the target for the trial experimental therapy. Because many molecular alterations are rare, fewer patients are enrolled. This has led to trials being forced to be multicenter and multinational, including trials in Latin America. This article discusses the challenges and opportunities to conduct precision oncology trials in Latin America, aiming to help sponsors and investigators to solve complex issues that ultimately lead to more of such trials being run in the region, potentially benefiting more Latin American patients with cancer.

INTRODUCTION

The global movement of interactions of companies, citizens, and governments from different nations toward clinical research activities has gained consistency in the last decades. The largest average annual growth in clinical trial participation occurred in lower-middle-income countries (LMIC; 33%) and low-income countries (LIC; 21%) [1], with Asian and Latin American countries showing the largest increase (30% and 12%, respectively), and three Latin American countries were ranked among the top 25 countries with higher participation in pharmaceutical clinical trials: Argentina, Brazil, and Mexico [2]. Yet conducting clinical research in LMIC and LIC

needs several considerations. Two decades ago, concerns were raised because of previous research experiments in Africa. Trials with azidothymidine (AZT) to prevent human immunodeficiency virus vertical transmission were considered unethical because AZT was not accessible in Africa at that time and the comparator was considered placebo [3]. This historical example brings up the principle that the ethics for trial design and conduct are universal. The application of ethical principles to research in developing or emerging countries requires the support and involvement of the host country as well as an understanding of how conditions in the host

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country may differ from conditions in the partner countries. Consequently, different types of clinical trial designs and the proper selection of the comparator intervention should be carefully evaluated by research actors in LMIC and LIC [1, 4].

Precision oncology trials (POTs) bear the concept that using molecular information about patients and their diseases enriches participants' selection for a given trial [5]. The use of a "new taxonomy" that defines diseases by their underlying molecular drivers to guide targeted therapies holds the promise to deliver superior outcomes to patients [6]. Participation in POTs needs to fulfill molecular-based selection criteria, which strongly limits accrual, and as a consequence, screening successes have decreased, costs have increased, and fewer subjects are enrolled [7, 8]. To recruit a selected patient population, studies have become multicenter and multinational to reach a larger pool of potential research participants. Therefore, globalization of POTs is necessary to allow faster trial enrollment and to shorten the timelines for clinical testing completion [9, 10]. But precision oncology clinical trials carry a complex structure that requires multiple and specific stakeholders: genomically stratified population, next-generation sequencing (NGS) scientists, bioinformaticians, biotechnology companies, governmental staff prepared to regulate biotechnology and to handle innovative products, investors, attorneys with expertise in clinical trials, genomics and human genetics applications, health care payers, and others. Given the globalization of precision clinical cancer research and the need to include more regions other than Europe and the U.S., is it feasible for those trials to be conducted in Latin America?

GENERAL ETHICAL ASPECTS THAT REGULATE CLINICAL RESEARCH—PARTICULARITIES IN LATIN AMERICA

The current ethical and regulatory system for research activities involving human subjects were developed in response to deliberated abuses in the past, in which the most infamous were the Nazi Medical World War II crimes and the experiments conducted on black people in Tuskegee, Alabama. Ethical guidelines in human protection are constantly overseen by the Declaration of Helsinki (DOH; which was last updated in Brazil in 2013). And ethical codes have become the basis for clinical research regulations, such as the Nuremberg Code (1947), the Belmont Report (1979), the International Conference of Harmonization and Good Clinical Practice (ICH-GCP; 1996), and the Council for International Organization of Medical Sciences (2002), which have been adopted by several nations and by Latin America in the "Documento de las Américas" of the Pan American Health Organization [11].

An essential requirement of any clinical research is to guarantee that patients accept participation voluntarily and that ethical bodies critically review the scientific protocol and consent forms. Patient subjects must be fully aware of protocol procedures and must understand properly the risks and benefits involved. They also have to be informed about treatment alternatives, if applicable. The information provided in the informed consent form (ICF) must be objective, adapted to local culture, and presented in lay terms. The process of signing the ICF should avoid any possibility of coercion, even if unintentional. ICFs from multinational trials

often contain an enormous list of potential adverse events, which are described in medical terms such as "neutropenia," "hand-foot skin reaction," and "increase in QT intervals." In POTs, genetic tests are sometimes described in detail, making ICFs even more difficult to understand [12]. This is of particular concern in low socioeconomic settings [13, 14] and when there are language barriers, as, for example, in some populations in Latin America such as the Quechua-speaking people in Peru, where the presence of an institutional or patient-related translator is necessary. Additionally, high illiteracy rates and low educational status in some areas in Latin America are extra pitfalls [15].

Technology can be used to improve the informed consent process. Besides written information, visual techniques such as graphics and/or videos can be provided in electronic informed consent devices (e-ICFs) in order to leverage the comprehension of fundamentals of POTs [12]. In fact, the last version of the ICH-GCP guidelines was revised to highlight the current global level and the even more complex protocols as well as the potential usefulness of digital applications such as mobile and real-time data capturing systems.

PRECISION ONCOLOGY TRIALS AND THEIR CHALLENGES

After the publication of the Human Genome Project in 2003, we witnessed an explosion of knowledge, technology, and studies pushed by the new paradigm of the genome era. The concept of cancer as a single disease remains in the past, and instead, we now recognize a constellation of diseases that can be divided into multiple subtypes based on genetic, proteomic, metabolomic, and epigenomic profiles. The movement toward the personalized treatment and better prediction of therapeutic responses has led scientists to adopt the term "precision medicine" to refer accurately to the use of genomic tools in human research, risk assessment, diagnostic categories, and therapeutic strategies in medicine. The NGS technologies (using DNA, RNA, or methylation sequencing), genetic computational solutions for omics data, and large-scale biologic databases such as The Cancer Genome Atlas and the Catalogue of Somatic Mutations in Cancer [16] have unfolded new perspectives on how to precisely attack malignancies, uncovering novel genomic signatures and targetable key genomic changes in the tumors. Thus, the acceleration of precision oncology holds a great hope not only for the most common cancers but also for rare subtypes.

(Re)use of Human Biological Sample and Its Genomic Data

The concepts and utility of POTs are apparently in place; however, this is just one part of a larger picture. For many decades, tumor biological samples were collected once at diagnosis, and small biopsy fragments were enough for hematoxylin and eosin staining and a few immunohistochemistry markers. Currently, more biological materials at multiple timepoints are necessary for diagnosis, molecular characterization, and evaluation of response to targeted therapy. In addition, promising markers emerge every day from translational research, bringing up new challenges to ongoing trials that will have to incorporate each of these new elements to the research enterprise. Some Ethics Committees request a specific informed consent

including all the biomarkers to be analyzed. This ICF often becomes obsolete and inappropriate for use in unforeseen secondary research aims, imposing an enormous obstacle to the reuse of collected material [17]. In addition, the majority of sample collections are project-driven collections (“biorepositories”) that restrict their use to a single researcher or a single research group. The use of tumor banks could overcome these challenges. Donors providing samples for biobanks have the option to provide a general consent, in lieu of a consent for each new research project. Although biobanks are increasingly recognized as vital to developing cancer research, few biobanks exist in Latin America. With the exception of Brazil, research tumor banks in other Latin American countries operate without specific regulation (Table 1).

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Genomic Data Handling and Privacy/Discrimination Concerns

Generation and analysis of genomic data require expensive and sophisticated equipment and highly trained personnel that are restricted to some research centers and are not widely available in Latin America [18]. To generate comprehensive data on Latin American patients with cancer, POTs should be collaborative and preferentially multinational. The amount of genomic data generated currently by research is enormous, and it is desirable that results are shared in public databases. The aim is to translate this huge amount of data into clinical practice, and the big challenge is how to do this while assuring the privacy of the participants and the confidentiality of their genetic information. In other words, genomic and clinical characteristics should be available and anonymous at the same time, never allowing the link between a specific research participant and his/her genetic information. Issues with the maintenance of privacy, data security, and confidentiality of research-related genetic information have raised ethical concerns, and the absence of clear regulations or policies may impair the recruitment of patients into future POTs.

From patients’ perspectives, concerns with confidentiality are related to potential use of genetic information for discrimination, as, for example, when applying for a job or purchasing health insurance. Such risk is related to sensitive information on a patient’s genetic background (e.g., germline mutations or polymorphisms) but that has a faint association with tumor genetic alterations (e.g., somatic mutations, methylation, mutational burden, etc.).

Recently, a Brazilian law to protect individual data will come into force in the next 2 years (PLC 53/2018). The objective is to safeguard privacy rights to individuals. Clearer requirements would be necessary for collection, storage, manipulation, and sharing of personal data with companies while promoting technological development. An important aspect to be regulated

involves making authorizations to study personal data more flexible [19]. Although this Brazilian law constitutes progress, there are no specific legal protection initiatives against genetic discrimination by employers, health insurers, and others in Latin America such as the Genetic Information Nondiscrimination Act passed into law in 2008 in the U.S. [20].

Access to Health Care and Novel Targeted Therapies

The selection of participants in POTs is not efficient as many have to be screened to identify the eligible participants, but the tumor response rates tend to be higher. For example, it is estimated that only 1.5% of patients with relapsed and refractory solid tumors will benefit from targeted drugs for identified mutations [8]. This should be clearly explained to candidates in the consenting process. Moreover, once clinically relevant genetic information is available, for example, when a druggable mutation is revealed (i.e., crizotinib for *ALK* translocation), investigators have the ethical obligation to indicate the best treatment based on this new information while halting any clinical research activity [21]. However, most targeted therapies are expensive and may not be accessible to many patients. For example, the advances in the molecular profiling and treatment of non-small cell lung cancer over the last 10 years have not equally benefited patients worldwide. In Latin America, a very bureaucratic drug regulatory approval process, affordability of extremely expensive targeted therapies, and lack of widespread access to genetic diagnostic tools pose huge challenges to the access of adequate lung cancer treatment [22, 23]. This situation, particularly in countries like Brazil, Argentina, Ecuador, and Uruguay, where the state by law has to provide comprehensive, universal, and equal access to the health care system, may trigger lawsuits against the government to pay for unaffordable (and sometimes, experimental) drugs [21, 24]. Paradoxically, the judicialization of health care increases inequity in access to drugs because it is not pursued by citizens who can’t afford a lawyer [25].

Patients’ Preferences and Values

From a patient-centered perspective, personalized medicine should consider broader aspects of patient preferences and values [26]. In Brazil, where great emphasis is put on physicians as decision makers, the survival time is more valuable for patients with cancer than for health care professionals, whereas quality of life is more important for health care professionals than for patients with cancer [27]. Behavioral sciences are examining patients’ attitudes and preferences to understand the engagement in treatment decision making [28]. And patients’ individuality strongly influences, if not determines, treatment decisions. Evidence per se is not enough, and one has to consider how patients envision the outcomes related to current standard of care (SOC) practices (efficacy, quality of life, safety) to make clinical judgments and decisions, including the decision to enroll in a clinical trial [28, 29]. In this aspect, the individualized approach of POTs, with recruitment usually based on biomarkers, is associated with high expectancies of success and lower tolerance of uncertainty for a given study outcome. However, even if a new therapeutic strategy is supported by a strong background and rationale on molecular mechanisms and

Table 1. Latin America tumor banking requirements per country

Country	Regulation	Tissue collection	Quality
Brazil	Brazilian Ministry of Health Ordinance 2201/11 and the National Health Council Resolution CNS 441/11 regulates ethical and operational issues. It is expected that any biological samples need patient authorization for tests. Multinational biorepositories should be accessible to local investigators and not limited to Brazilian samples.	Institutions have developed internal protocols for sample collections, but for certain targets, the protocol might not be suitable.	The quality control to define the best practices of preservation of macromolecules is not well determined. Pathology quality of tissue samples are key standard of tumor samples.
Peru	Law N° 28189: general law of transplantation of human organs and tissues and Health Resolution DS N° 001-BTT-DP-DISAD/ INEN. There is no specific regulation for biorepositories or biobanks.	Biorepository should be linked to internal protocols for sample collections.	Quality should follow international standards. No specific local standards are needed.
Argentina	Currently, there are no specific regulations for biobanks except for those meant for therapeutic uses (Resolution 607/07, National Ministry of Health). Clinical investigation, including access to and use of biospecimens for research purposes only, has to follow the Resolution 1480 – Guide for Research with Human Subjects- of the National Ministry of Health and Social Development, and other provincial /local regulations, such as Law 3301 of the City of Buenos Aires or Law 11044 of the Province of Buenos Aires. Management of data linked to biospecimens has to follow the ruling of the National Law 25326 for Personal Data Protection. During 2018, the National Ministry of Health and Social Development, through the National Advisory Committee on Research Ethics, began a collaboration with the Ministry of Education, Culture, Science and Technology, through its ad hoc Commission of Biobanks for Research, to elaborate specific regulations for biobank creation, maintenance, and governance, including informed consents and material transfer agreements. The aforementioned ad hoc commission has already published a preliminary document of Recommendations for the Organization and Operation of Research Biobanks and Centers of Biological Resources [53].	Tissue collection currently is managed according to internal procedures. Some biobanks such as the ones participating in the Latin America Cancer Research Network [54] follow procedures based on The Cancer Genome Atlas bio specimen management protocols.	Most current biobanks are based on formalin-fixed paraffin-embedded specimens. For the very few that collect fresh frozen samples, quality assurance actions include continuous temperature monitoring. Quality control of molecular derivatives (DNA, RNA) usually follow state-of-the-art quality controls.
Ecuador	For interventional studies, biological samples are regulated by the Agencia Nacional de Regulación, Control y Vigilancia Sanitaria. There is no specific regulation for biorepositories or biobanks.	Institutions have developed internal protocols for sample collections.	Quality should follow international standards.
Uruguay	The Uruguayan government decree 379/008 regulates the use of biological material and data obtained from research. Moreover, the law 18968/2012 states that the Ministry of Public Health - National Institute of Donation and Transplantation of Cells, Tissues and Organs - authorize programs for therapeutic and scientific purposes and activities that use cells, tissues, and organs of human origin, from donations. Related ethical issues are regulated by law 18335/2008, and law 18331/2008 establishes the principles of personal data protection. There is no specific regulation for biorepositories or biobanks.	Institutions have developed internal protocols for sample collections.	The quality of tissue samples and the preservation of macromolecules follow international standards [55, 56].

(continued)

Table 1. (continued)

Country	Regulation	Tissue collection	Quality
Chile	The laws 20.584 (rights and duties of patients) and 20.120 (research with human being and the human genome) regulate ethical and operational issues. It is expected that any biological samples stored for research purposes require a signed consent form from patients, authorizing the use for research of his/her samples. There are no restrictions for tissue samples, of an approved study, to be transported to a central lab. There is no specific regulation for biorepositories or biobanks.	Protocol-specific standard operational procedures are in place for sample collection, transport, and storage, following international recommendations.	Within a research project, the quality control is specified, following international recommendations. Tissue samples taken for routine practice could suffer more variations in terms of processing and storage conditions (applicable for formalin-fixed specimen).
Colombia	The delivery of health care in Colombia must comply with the resolution 2003 of the year 2014 promulgated by the Ministry of Health. This law includes broad provisions for the collection and handling of tissue samples. Most institutions voluntarily abide by the recommendations of the American College of Pathology. Clinical research is also regulated by the Ministry of Health (resolution 2378 of the year 2008), in which Colombia adopts the international Good Clinical Practice Guidelines as the minimum standard required for any person or institution engaged in research with medications in human subjects. The enforcement of this law is the responsibility of the Colombian agency for the vigilance of foods and drugs (INVIMA). There is no specific regulation for biorepositories or biobanks.	Sample collection can be performed by physicians and other qualified health professionals (nurses, laboratory technicians, etc.). Sample storage is allowed and can be hosted in different facilities such as tissue banks, clinical pathology laboratories, hospitals, and outpatient facilities. Difficulties arise when tissues need to be shipped abroad because many carriers refuse to do so on the basis of a presumed potential biohazard. Those carriers who accept to transport samples charge extremely high fees.	Other than the Good Clinical Practice guidelines, Colombia lacks other country-wide quality standards in research. The INVIMA conducts extensive and exacting audits of the clinical research centers. Noncompliance with the Good Clinical Practice guidelines may be grounds for research center closure. But the INVIMA is woefully understaffed, so universal research quality cannot be assured.
Costa Rica	Biomedical research is regulated by the national resolution no. 9234. The Costa Rican Ministry of Health is in charge of auditing and monitoring the medical research by the National Council for Biomedical Research. There is no specific regulation for biorepositories or biobanks.	Private and public institutions across the country collect tissue samples using a “banking model.” Usually, such tissues are collected and processed as paraffin blocks and stored in pathology repositories.	Quality should follow international standards.

Abbreviation: INVIMA, Instituto de Vigilancia de Medicamentos y Alimentos.

preclinical evidence, adequately powered trials are often needed to confirm efficacy and safety of a new targeted drug [30].

Thus, clinical trials in the era of precision medicine still take participants on a journey with essentially unknown outcomes. Potential adverse effects, chances to be assigned to control arms with placebo or with SOC drugs, and high likelihood of being deemed not eligible because of biomarkers restriction may influence patients' motivation to enroll into POTs. It is important to present the aforementioned scenario a priori to patients and to referring physicians to help them to guide their decision on whether or not to refer or to enroll in a POT. Valid and easy-to-understand ICFs/e-ICFs definitely aid in this time-consuming process that requires caution, attention, and respect for patients' needs and cultural beliefs.

LATIN AMERICA CLINICAL RESEARCH ENVIRONMENT

Conducting precision trials in Latin America is undoubtedly a great opportunity for scientific advances. Middle America comprises a population of approximately 50 million people,

of whom approximately 50% are ethnically characterized as admixed (Mestizos). Reports regarding molecular autosomal estimates of parental ancestry indicate that Amerindian ancestries are prevalent in Mexico and Guatemala, whereas in the Caribbean area, African ancestors predominate. South America has approximately 422 million people, and the influence of European and Asian ancestry is more marked in this region. Because of this rich mixture of ancestry, Latin America presents a unique population for clinical, social, environmental, and genetic characteristics in cancer research.

Cancer epidemiology in Latin America differs from that found in other regions, having, for example, higher incidences of gastric, cervical, and gallbladder cancers [31, 32]. The region also combines modern medical facilities, well-trained investigators, and premier research groups. Although most Latin American investigators and study coordinators have no formal training in clinical research [33], those who work in large academic centers generally learn the concepts of clinical cancer research through practice and international training and/or networking. National cooperative groups have

facilitated the participation of Latin American sites in global academic research initiatives, such as the Chilean Cooperative Group for Oncological Research and the Peruvian Cooperative Oncology Group, which is an active member of the Breast International Group and the International Breast Cancer Study Group. Multinational initiatives of specialized research groups such as the Latin American Cooperative Oncology Group, the U.S. Latin American Cancer Research Network, and the Latin American Cancer Research Network [34] are contributing to the capacity building for high-quality research participation in the region [33, 35]. Clinical oncology groups also promote discussions and improvements fostering local development of research activities such as the Latin American Society of Clinical Oncology and the Latin American Federation of Societies of Cancerology [36]. Despite these efforts, the activity of clinical trials in Latin America represents only 5.3% of all clinical trials worldwide. For cancer trials (neoplasm, tumor, malignancy, oncology, neoplastic syndrome, and neoplastic disease), Latin America represents 4.0% of the global activity (source: clinicaltrials.gov on October 28, 2018). Reasons for such low numbers are numerous. For example, Brazilian authorities classify clinical research activities as risky drug trials, and the regulation for human research is the same for all types of research—from pharma-sponsored phase I–III trials to academic studies. Such requirements in oncology trials result in very high costs for simple studies that are almost prohibitive for academic studies; thus, they end up becoming pharma-sponsored trials [37].

Education Level and the Understanding of Informed Consent Forms

Latin America comprises low- and mid-per-capita-income countries in a quite heterogeneous scenario [38]. Limited access to education results in a high percentage of illiteracy. Although it is common knowledge that most patients consider the ICF difficult to understand, in LIC and LMIC, this scenario is likely to be even worse [10, 13, 39]. Such unequal economic distribution and heterogeneous educational background is a critical combination that may result in recruitment of potentially vulnerable subjects. Such individuals' freedom and capability to protect themselves from intended or inherent risks is variably abbreviated, from decreased freewill to inability to make informed choices [40]. For example, we performed a transversal study to evaluate the readability and complexity of ICFs of phase III cancer trials using widely available software (Flesch Index and Flesch Kincaid Index) among 137 patients with cancer who had been enrolled into clinical trials in an academic center in Sao Paulo, Brazil. We found that the complexity of the ICFs required at least 18 years of education, whereas half of the patients had attended less than 8 years of school [15]. Such results provide a clue of the unrealistic content of the ICFs (required by regulatory agencies) and to understand the misconception of human beings used as "guinea pigs" [36].

National Cancer Registries and Geographic Distribution of Cancer Care

Another regional problem is the paucity of accurate cancer registries [41]. Cancer registries provide the data-driven foundation for cancer control efforts. Innumerable initiatives

for the systematic collection, storage, analysis, interpretation, and reporting of data on subjects with cancer are being done in Latin America. Uruguay, for example, besides having a cancer registry with nationwide coverage (run under the Comisión Honoraria de Lucha contra el Cáncer), has developed and implemented the national Oncology Electronic Health Record that includes information about genetic and nongenetic risk factors, tumor molecular profile data, and clinical-pathological characteristics. The Argentinian National Cancer Institute has made progress in establishing national computer registers on types of tumors (the RITA registry), cases of pediatric oncology (ROHA), epidemiological surveillance (SIVER-Ca), and the recently created SITHER, which collects reported cases of tumors with hereditary and familial characteristics. This model served for diagnosis of weaknesses and difficulties in carrying out molecular epidemiology projects. The new Brazilian law (PLC 14/2018), dated June 25, 2018, establishes that any and all cancer-related health and disease events will now have mandatory notification in public and private health services throughout the country [42]. The law takes effect in 180 days after the due date and requires regulation from the Ministry of Health. However it will take some time for this to become reality because the law requires investments and training on the part of academic institutions.

Despite these initiatives, accurate and robust cancer registries are still under development in several Latin American countries. Of note, most patients with cancer in Latin America are treated in large academic public institutions, where most clinical trials are also conducted. Centralizing cancer treatment and trials in big centers (often in major cities) provides a more homogeneous oncologic care and consistent setting for trial enrollment in terms of therapeutic protocols, technology, working staff, and quality data for cancer registries. Nevertheless, such a strategy also reduces access to oncologic care and may limit patient recruitment and cancer registries in rural areas. In countries such as Peru, Ecuador, and Bolivia, for example, more than half of the population live in the rural countryside.

Genetic Research and Regulatory Agencies

Research regulation in Latin America has been developed for decades, but still, for some countries such as Brazil, it has one of the longest timelines for a trial protocol review and approval. Many efforts have been made to enable good and faster regulatory review, but in the case of genetic data handling, the requirements are sometimes unpredictable [43]. The review directives upon ethical principles may also vary considerably across Latin America, depending on the institutional experience. Genetic research projects submitted to ethics committees may be delayed if the committee is not familiar with the theme.

In terms of technology, research sites also vary considerably. Laboratories proficient in next-generation sequencing and other genetic tests performed under fast-delivering logistics are limited to few academic institutions or private laboratories. In 2017, only 221 next-generation sequencing platforms developing cancer genomics projects existed in Latin America [44]. Thus, samples collected in global studies end up in central laboratories usually located in developed countries with generation of a multinational biorepository. In this scenario, the regulation for the use of samples (rights and

limitations) and the administrators' responsibilities over the samples pose obstacles to reaching consensus among research collaborators and regulatory agencies. Moreover, the regulation of sample-derived genetic data sharing is in its infancy in Latin America. A big effort is being made in Argentina regarding training of institutional review boards about genomic data information and analyses through the recent creation of the National Ethics Advisor Committee, which is in charge of establishing the basic criteria for ethical evaluation of clinical research, including genomic data manipulation. This Committee has a specific Advisory Commission for Biorepositories and Genomic Data, in which genomic researchers, clinicians, and ethicists are currently discussing the minimal requirements needed for good quality and ethics aspects of running precision medicine research in the country. In Ecuador, the government has also created the Ethics Advisor Committee to facilitate the undertaking of research.

Recommendations involving data privacy and confidentiality of individual identity are key points of data handling. In that sense, Argentina is currently updating its law on personal data handling with a chapter devoted to genomic information. Therefore, researchers are encouraged to obtain consent for future use and broad sharing of genomic and phenotypic data, balancing the responsibility of protecting participants' interests with the potential loss of opportunities for future research. In Uruguay, the government constituted a National Commission of Ethics in Research, whose main responsibility is to examine the ethical aspects of research with human beings and to update and adapt the applicable regulations.

Precision Randomized Placebo-Controlled Cancer Trials in Latin America

The use of placebo is a well-recognized method to control for observation bias [45]. Placebo responses consider an individual's genetic predisposition, personality, type of disease (e.g., tumor with spontaneous shrinkage), and values that could also interfere with therapeutic outcomes [5]. Thus, such factors justify the use of placebos in POTs. Brazil is the Latin American country with the largest number of clinical trials [2, 46]. It is also known for its strong opposition against the flexible use of placebo. Both the Federal Council of Medicine and the National Health Council have published resolutions regulating the use of placebo exclusively in clinical trials, preventing their use if there is any effective therapeutic method already in place [47]—although sometimes the interpretation of “effective” by this council is not standard. Likewise, in Uruguay, the current national regulations adhered to the 2000 version of the DOH without taking into account subsequent revisions, which flexibilizes the use of placebo and the best existing treatment in controlled clinical trials (article 29 of the DOH).

The use of placebos also represents a known barrier to trial enrollment. If compared with U.S. patients with cancer, Brazilian patients with cancer demonstrate lower interest in participating in POTs. In a cross-sectional survey with Brazilian patients with cancer and investigators, authors observed that 41% of patients were not willing to participate in trials with a placebo-exclusive arm, and half of investigators objected to recommend a POT to patients because they “felt uncomfortable to offer no treatment to their patients” [48, 49].

POTs in Latin America and the Use of High-End Next-Generation Sequencing Technology

POTs are able to gather elements in clinical data to classify and measure associations between environmental exposures, clinical consequences, and genetic profile. The analyses of the large amount of data generated need a technological approach to integrate any data from a myriad of distinct sources; this is a key solution to refine patient particularities, but will create a tremendous volume of information that would cause conventional processing methods to simply collapse. Big Data analytics covers data retrieval and handling and analyses of massive, diverse data sets of genomic and clinical data. An analytic result may reveal hidden patterns, uncryptic not obvious correlations, and many other types of patterns (or lack of any) [50]. Precision trials would frequently need to find a specific patient in a huge population or the study should be placed in a particular population with higher probability for eligible candidates.

Latin America's leading markets have a proven appetite for technology adoption. Brazil (at number 2 in the world), Mexico (6), and Argentina (8) are among the highest-ranked markets worldwide in time per week spent on the internet, much of it on mobile devices [51]. Technology companies are also fast growing in Argentina, which is on the verge of a boom [52]. This is a particularly good scenario to run POTs in Latin America in the field of patient recruitment, as these patients are likely to better accept digital language and innovative approaches using high-end sequencing technology. However, Latin America currently needs improvements in local accessibility of biotechnology suppliers, particularly in genomic analysis, to centralize and coordinate multinational trials [36].

The lack of local quality reinforcement regulations also plays against the necessary investment on quality assurance of public and private genomic analysis providers. Political decisions regarding protective economic rules for locally developed tests and more strict quality controls should be necessary to assure the necessary genomic analytic capabilities.

With respect to molecular analyses of tumors, Latin America faces difficult challenges in implementing integrated analysis of germline and somatic variants in cancer care. In Argentina and Brazil, for example, both private and public institutions suffer from the high cost of imported standard lab equipment and molecular biology reagents for precision medicine especially when large-scale purchases for analysis cannot be guaranteed. Even when infrastructure and equipment as well as expert human resources can be attained, local high-quality genomic analysis is hard to sustain because of the aforementioned costs. The lack of local quality reinforcement regulations also plays against the necessary investment on quality assurance of public and private genomic analysis providers. Political decisions regarding protective economic rules for locally developed tests and more strict quality controls should be necessary to assure the necessary genomic analytic capabilities.

Table 2. Recommendations to improve the participation of Latin America in precision oncology clinical trials

Aspect	Recommendations for improvement
Ethical	Local investigators should be qualified to be the primary stakeholder to evaluate whether the trial is adequate/ethical to be conducted in the institution, according to international standards and current local regulations. The local investigators are the critical staff to understand the local culture to predict patient protocol adherence, access to infrastructure, and known staff competencies. This information should be taken into consideration in the decision-making process during the feasibility analysis of trials. This analysis should be prior to regulatory submission. The role of the investigator is to guarantee the viability of study conduction in his/her institution. It is strongly advisable to make the feasibility analysis process in collaboration with other institutional staff, such as biobank coordinator or a clinical operations coordinator. All efforts should be made to obtain a valid informed consent through a complete comprehension of the research by the candidates. As per GCP, the language should be <i>as non-technical as practical and should be understandable to the subject (ICH GCP 4.8.6)</i>. Sponsors and regulatory bodies should allow and stimulate ICF to be linguistic and culturally adapted by local investigators; for international ICFs, we recommend that a separate translated and culturally adapted version be used, with the approval of local IRBs. The cultural adaptation could be performed by one or two principal investigators of each country, after discussion with sponsors. Although the ICF has to contain all clinical trial information in lay terms, the document needs to be reduced in terms of amount of unnecessary information (e.g., risks associated with interventions routinely performed by patients with cancer, such as blood counts and computed tomographies). The informed consenting process should be easily renewable (by using electronic consent, for example [12]) when new medically relevant information becomes available; for example, when participants donate samples for biobanking, an electronic consent process could be applied as the system can update patient consent immediately in case of changes in participant decision, and participants could also have the right to track their samples, as they could receive electronic updates on new research initiatives [57]. In the era of new trial designs that are essentially dependent on biorepositories, it is highly recommendable to update technology approach, especially in terms of e-ICF. The use of electronic devices and technology is irreversible and another point to consider as to be globally competitive. Investigators and sponsors must be educated and prepared to provide transparent information about the use of unrestricted redisclosure of data, informing participants about the risks of breaching anonymity/privacy/confidentiality [58]. Trial participants need to be informed about the possibility of incidental genetic findings during the study that may affect their treatment strategies. If the protocol intent is to investigate genes that indicate a molecularly targeted effective therapy, a feasibility analysis of the protocol should include access to drugs that are commercially available in the given country. This is because in some countries, like Brazil, the National Ethics Committee resolution recommends the sponsor to provide commercially available matched drugs once a molecular target is identified, even if the study is not interventional; the therapy has to be provided for as long as the patient benefits from it, according to investigator's discretion. In the case of genetic studies where known germline mutations are encountered, genetic counseling should be offered freely to participants and guaranteed by the investigators—this may be problematic in the case of mutations of unknown significance. Participants need to confirm their comprehension that data sharing among researchers is intended.
Training	All personnel involved in clinical trials, mainly investigators, must receive formal and continuous high-quality training with special focus on POTs [59]; this could be provided by institutions participating in clinical trials with or without industry financial support. A comprehensive work of updated education on POTs has to be guaranteed for the different members of local institutional review boards, including recent international updates of legislations; this could be provided by institutions (investigators included) participating in clinical trials. Staff training to use technology would be a critical aspect to run POTs. Clinical data coordinators and/or bioinformaticians experienced in accessing genetic and clinical databases are highly desirable. Less experienced institutions should participate in collaborative groups across Latin America to exchange knowledge with experienced centers.
Regulatory	POTs should be submitted to regulatory authorities with a dossier including declarations of study promoters, sponsors, and investigators stating complete adherence to ethical recommendations and how they guarantee such compliance. Investigators should anticipate all requirements stated in local regulatory recommendations, especially regarding the use of genetic data as to avoid delays. Efforts should be made to speed up the process of trial approval in Latin America, considering the elimination of the redundancy of having local and central IRBs (e.g., Brazil) and establishing fair but quick timelines for trial assessment by regulatory agencies. Limit protocol translation (and linguistic and cultural adaptation) to the ICF, allowing the acceptance of all study protocol documents by regulatory authorities and local/central IRBs in English, as a universal language, to expedite regulatory approval. Local biorepository may be administered by a local institution under local agreement. A multinational contract agreement is recommended when sites in Latin America and Europe/U.S. use biological samples. In any case, an agreement should include detailed aspects of rights to use samples as well as patent and publication policies. This agreement may be subject to regulatory and ethical approvals.

(continued)

Table 2. (continued)

Aspect	Recommendations for improvement
Infrastructure	POTs should be evaluated from several perspectives beyond scientific and ethical standards, such as adequate infrastructure, comprehension of local epidemiology, adequate level of training of the research staff involved, and capacity to articulate distinct departments. National cancer registries and safe electronic databases need to be developed and/or improved to provide epidemiological information; this could start as pilot projects in large academic centers. Although Latin America has a high technology appetite, it is important to access candidates' digital background as they would need to use mobile devices, for example. If a study candidate has no clear capacity, a caregiver might be considered to help with technology use. Discuss strategies to increase local laboratories' capacity to perform germline and somatic molecular analyses with high-quality standards to facilitate patient enrollment and reduce costs. This is important to boost molecular diagnosis (and all related activities, such as personnel training and job creation) in the region. Care must be taken to enforce quality control/assurance procedures as well as to encourage related standard operating procedures in genomic laboratories, for both data generation and interpretation. There should be tax policies aimed to encourage biotechnology in Latin American countries. Governmental initiatives to reduce standard lab equipment and molecular biology reagents taxes under certain circumstances could foster the development of local staff and facilities specialized in next-generation sequencing technology. Importation of research-related materials should follow specific expedited processes (and not be lumped together with importation of agricultural products, for instance, as demonstrated in Table 1).
Cultural	Key cancer centers across countries have the duty to educate their patient population on the risks and advantages of participation in POTs to prevent barriers such as the "guinea pig" myth. When there is not any effective therapeutic method to compare with the experimental one, the placebo-controlled trial should be encouraged. However, as Latin American populations likely have lower willingness to participate in placebo-controlled precision trials, we encourage the use of unbalanced randomization (2:1 or 3:1 allocation ratio) to lower chances of placebo-only arm allocation when feasible.

Abbreviation: e-ICFs, electronic informed consent forms; GCP, Good Clinical Practice; ICF, informed consent form; ICH, International Conference of Harmonization; IRBs, institutional review boards; POTs, precision oncology trials.

As for routine molecular diagnosis, several pharmaceutical companies have until recently used a business model in several Latin American countries, including Argentina, Colombia, and Brazil, based on provision of the companion diagnostic assay used to guide prescription of targeted drugs. However, this model is currently being changed to a market-based, competitive approach, in which competitive providers of private medicine purchase such genetic tests before allowing coverage for the targeted drug. This strategy would be beneficial in terms of assuring quality but more difficult in terms of provision for local laboratories. In Colombia, these industry-sponsored mutation analyses of some genes (i.e., *RAS*, *EGFR*, *BRAF*), although widely available, are concentrated to a few laboratories in major cities, with long waiting times between test request and results. Additionally, there is general poor access to rare clinically relevant mutations without appeal to big pharma. From the practical point of view, only centers equipped with access to technology are in a position to run POTs in Colombia, mostly located in Bogotá, the capital.

Lastly, another barrier for successful enrollment in POTs stems from the way cancer care is reimbursed to treatment providers. Fee-for-service is the predominant reimbursement model in some Latin American nations, such as Colombia and Brazil, which may disincentivize some treating physicians to refer patients to a different center.

Recommendations to Overcome the Challenges and Improve the Participation of Latin America in POTs

In spite of all these caveats and challenges, some Latin American institutions are already capable of conducting POTs. We describe biobanking requirements per country as to facilitate collaborations with those Latin American countries

(Table 1). To expand the conduct of POTs to more Latin American centers, some crucial obstacles have to be overcome. Below, we propose an expert panel list of recommendations (Table 2) and potential solutions to boost the dissemination of POTs in our region. Three authors (R.J.A., R.S.C.G., and R.R.) initially contacted key research leaders in their Latin American countries to discuss the manuscript and recommendations. Because this project did not receive or have financial support, we conducted all discussions by teleconference and e-mails. All recommendations and requirements were carefully revised and approved by the authors. Each author described their local regulatory characteristics (Table 1).

CONCLUSION

POTs involve a complex scenario that is not limited to genetic and clinical data handling. They need accessible technology requiring staff trained at a high level to interpret useful information. The ethical oversight has to be more dynamic and personalized to local environments while maintaining moral fundamentals. A comprehensive strategy should be applied that involves improvements in staff training, adaptations of infrastructure, updated investigators' ability to navigate in local regulatory environments, and better access to technology and health care. We conclude that POTs are feasible in Latin America but are still limited to few investigators and institutions from academic centers. Here we recommended some actions to personalize and boost POTs across Latin America. With the inevitable globalization of clinical cancer research, it is crucial to have Latin America on board in order to improve the external validity of trials' results and to provide more access to new drugs for Latin American patients with cancer.

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