Review Article

Characterization of clinical trials in Ecuador and their association with disease burden: Are there research gaps?

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Abstract

This study offers a detailed analysis of clinical trials conducted in Ecuador from 2010 to 2022 to assess alignment with the country's disease burden as indicated by the Global Burden of Disease study. Utilizing data from five registries, including ARCSA and Clinicaltrials.gov, we analyzed characteristics and coverage of 75 CTs after removing duplicates and ineligible studies. Findings reveal a 50% research gap across disease groups, with neoplasms being the only category matching disease burden. The scarcity of clinical research highlights the disparity between CTs and prevalent diseases such as cardiovascular and kidney diseases, diabetes, and other non-communicable conditions. Our results underscore the urgent need for increased clinical research investment addressing these critical health challenges in Ecuador.

Keywords: Clinical trial, disability-adjusted life years, Ecuador, global burden of disease, health research evaluation, research

Introduction

Since the 1990s, the implementation of clinical trials (CTs) has increased dramatically due to two main factors: the implementation of evidence-based clinical practices, a paradigm that led to CT being considered one of the studies with the highest methodological quality, degree, and strength of recommendation[1] and changes in international regulations for the marketing of pharmaceutical products, in which the presentation of efficacy and safety results through CT are mandatory for their approval.[2,3] In light of this increase and to promote good clinical practices, ensure the publication of results, and guarantee compliance with research protocols, multiple organizations have implemented CT registry databases [Table 1].[4]

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Most commonly, CTs have been implemented in developed countries with high economic and technological power, mainly related to the need for infrastructure, research centers, qualified personnel, supply of volunteers, and national regulations.[5] However, the globalization and internationalization of medicine, associated with the delocalization of CTs (multicenter-multinational studies), has increased the participation in these types of studies to countries in Latin America, Asia, and the East,[6] with sponsors being attracted mainly by the existence of less strict regulations, lower labor and infrastructure costs and different epidemiological conditions.[7]

In 2020, Latin America and the Caribbean were home to 4.6% of the world's CT, with Brazil, Argentina, and Mexico standing out with 1.3%, 1.0%, and 0.7%, respectively; however, the predominance of the major powers remains (USA: 38.8%; China: 5.2%, Spain: 4.8%).[8]

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Table 1: CT registration base

Registration base	Responsible organization	Characteristics	Year of onset	Link
International Clinical Trials Registry Platform (ICTRP)	World Health Organization (WHO). International Committee of Medical Journals Editors (ICMJE).	Free and accessible primary CTs registry. Grants a registration number. Accepts proposed, completed, and ongoing CTs.	2000	https://trialsearch.who.int/
International Standard Registered Clinical/ Social Study Number Registry (ISRCTN)	BioMed Central Ltd	Records of intervention efficacy studies (observational and CTs). It accepts registration of studies at any stage. It carries registration and search fees.	2005	https://www.isrctn.com/
Clinicaltrials.gov	United States National Library of Medicine (NLM) National Institutes of Health (NIH)	The registry of CTs, studies, and observation programs in the USA. Free and accessible.	2000	https://clinicaltrials.gov/
EU Clinical Trials Register (EU CTR)	European Medicines Agency (EMA).	Registration of CTs performed in the European Union or the European Economic Area. Free and accessible.	2004	https://www.clinicaltrialsregister.eu/
Pan African Clinical Trials Registry (PACTR)	Cochrane South Africa. South African Medical Research Council (SAMRC)	Open access platform. Regional registry of CTs performed in Africa. Allows manual registration (e-mail, letter, or fax) Free and accessible	2009	https://pactr.samrc.ac.za/
Chinese Clinical Trial Registry (ChCTR)	Western China Hospital. Sichuan University	Nonprofit organization. It includes CTs of Western and oriental medicine (acupuncture and moxibustion) performed in China.	2005	https://www.chictr.org.cn/enIndex.aspx
National Registry Agencies (Latin America)	Regulatory agencies in each country, for example, ARCSA* (Ecuador), ANIMAT** (Argentina), ANVISA*** (Brazil)	Registry of CTs performed in each country. Their registration usually carries a fee. Free access.	-	It depends on each country.

*ARCSA: Agencia de Regulación y Control Sanitario. **ANIMAT: Agencia Nacional de Medicamentos, Alimentos y Tecnología Alimentaria. ***ANVISA: Agencia Nacional de Vigilancia Sanitaria

In Ecuador, between 2010–2017, scientific production sharply increased, demonstrating a more significant association between the percentage of scientific publications and the leading causes of mortality (diabetes, ischemic heart disease, arterial hypertension, cerebrovascular accident, pneumonia, among others).[9] However, the association between CT execution and disease burden, which is of great importance, has yet to be assessed since there is evidence of a low association between the number of CTs and the most prevalent pathologies or disease burden in low and middle-income countries.[10,11]

Primary care physicians play a crucial role in understanding research gaps and advocating for the reallocation of resources to address these gaps in medical research. As the first point of contact in the healthcare system, they possess deep knowledge about the health challenges faced by their communities. Primary care physicians can become influential advocates for reallocating resources to align with local and national health needs by identifying areas lacking research. This advocacy effort has the potential to bring about positive changes in policy formulation and the allocation of funds for medical research, ensuring that critical health issues receive the attention they deserve.

However, the critical role of primary care physicians in research advocacy goes beyond identifying deficiencies in research. They actively shape policies and financial priorities that govern medical research funding. This involvement is particularly crucial in environments where research resources are limited and need to be directed to where they can significantly impact public health. By actively supporting research that addresses the prevalent health conditions in their communities, primary care physicians can ensure that clinical research is relevant and beneficial to patient care. This alignment between research and community needs enhances the translation of research findings into practical clinical interventions that improve individual and public health outcomes.

Materials and Methods

We searched the database of the Ecuadorian Registry of Approved Clinical Trials of the National Agency for Regulation, Control and Health Surveillance[12]; International Clinical Trials Registry Platform (ICTRP)[13]; European Union Clinical Trials Register (EUCTR)[14]; Clinicaltrials.gov[15]; BioMed Central International Standard Randomized Controlled Trials Number Registry (ISRCTN).[16] We identified all clinical trials registered from 1 January 2010 to 31 December 2022. Results were downloaded to Excel.

Based on the official title of the registered study, trials were categorized according to disease group, sponsor, year of registration, and ranked according to disease burden. In cases where the title suggested more than one disease group, the CT was included in all relevant categories.

Definitions

Disease burden: It was measured in disability-adjusted life years (*DALYs*), a value that represents the number of years lost due to illness, disability, or premature death.[17] To identify

Ecuador's disease burden, we based ourselves on the study *Global Burden of Disease (GBD) 2019,*[18] which measures the global disease burden tendency of 369 diseases and injuries in 204 countries between 1990 and 2019. Results according to each country are available on the Institute for Health Metrics and Evaluation (IHME) website, and the independent health research center located at Washington University, USA.[19]

Two types of disease classification were used, specific to the GBD 2019 study: level 1 aggregation, which groups them into seven categories, and level 2 aggregation, which groups them into 22 categories.

Research gap: Following previous studies by Aguilera[20] and Atal *et al.*,[11] a research gap was considered for a disease group when the proportion of clinical trials corresponding to this group (registered during the observed period) was less than 50% of the proportional disease burden that can be attributed to this group. For example, if in Ecuador, 10% of the disease burden corresponds to neoplasm, and the proportion of corresponding CTs to this disease group is less than 5%, there is a research gap. A partial research gap was identified when the clinical trial proportion in relation to the local disease burden was between 50% and 75%. Therefore, we consider that the research was aligned with the local disease burden when the proportion was over 75%.

Results

General description of the sample: A total of 122 registered CTs were found during the studied period; after the elimination of 47 duplicated items or those that did not meet the selection criteria, a total of 75 CTs were analyzed, out of which 24 were identified and included in the ARCSA official registry. The distribution of annual production is shown in Figure 1, which offers an increase in 2022.

Group and subgroup analysis: Regarding the sponsorship of the studies, it was verified that 47% of the CTs carried out in Ecuador were sponsored by the pharmaceutical industry. The main sponsor was the National Institute of Digestive Diseases (*Instituto Ecuatoriano de Enfermedades Digestivas* [IECED]) (20%), while other national institutions were responsible for 7% [Table 2].

Regarding research gaps, it was found that when considering level 1 of disease burden aggregation, there is a research gap in five out of the seven disease groups [Table 3], with only the categories of infectious diseases, maternal, neonatal, and nutritional diseases, and cancer being the only ones to be addressed in the surveyed CT.

Likewise, the level 2 aggregation analysis allowed the observation of a research gap in 50% of disease groups, of which 82% present a total gap [Table 3]. Within the first five groups with the most disease burden, it was verified that the neoplasm group is the only one that does not present a gap.

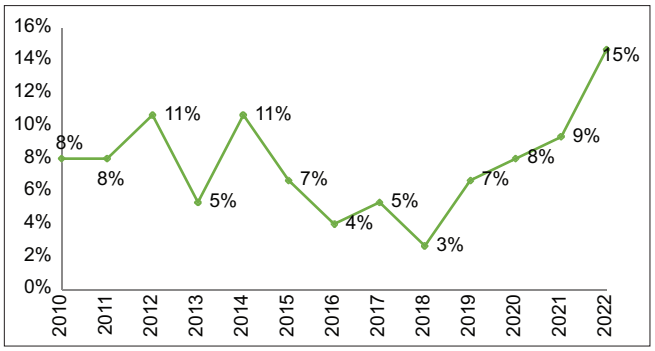

Figure 1: Percentage of CT registered by year 2010-2022

Other analyses: Of the CT sponsored by the pharmaceutical industry, 63.6% of the disease groups were found to have a research gap, with 92.9% having a total gap. [Table 4].

Discussion

This is the first report of this nature to be made in Ecuador, with the overall burden of disease using *DALYs*. Previous research has addressed the relationship between health studies in Ecuador and the leading causes of death in the country[9]; however, this does not evaluate disease burden entirely since it does not consider diseases that cause disability.

Our analysis found that the three most frequently studied diseases in Ecuador are non-communicable diseases (43%), CD, maternal, perinatal, and nutritional lesions (34%), and cancer (22%). According to Viergever *et al.*,[21] in their comparison between the registered CT and disease burden (measured through DALY), reported that the three most frequently studied pathologies worldwide are non-communicable diseases (52.4%), infectious diseases, maternal, perinatal, and nutritional (7.4%), and pathologies caused by injury (6.0%); which shows that, for the exception of cancer, the research areas covered in CTs mostly correlates with worldwide research. In Ecuador, the distribution of cancer research is led by breast cancer, with an incidence rate of 38.2 individuals per 100,000 people, followed by prostate cancer at a rate of 35.7 patients per 100,000, and cervical cancer with an incidence rate of 16 per 100,000. These rates are similar to those reported in Latin America and the Caribbean.[22,23] This focus on cancer aligns with the primary level of healthcare and underscores the importance of studying these conditions in line with the broader disease burden of the region.

The alignment between clinical research and primary care is critical. As the foundation of health systems, direct care services serve as the initial point of contact for individuals, families, and communities. They are well-positioned to address a wide range of health issues in an accessible, continuous, and coordinated manner. Due to frequent patient interactions, primary care providers have a unique understanding of community health needs and can advocate for research prioritizing prevalent and burdensome diseases.

Table 2: Amount of CT registered between 2010–2022 according to their sponsor

Sponsor	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	Total (%)
IECED	-	-	-	-	1	1	1	-	1	3	-	1	7	15 (20)
Hoffmann-La Roche	-	3	3	-	1	-	-	-	-	-	-	-	-	7 (9)
Sanofi	2	-	1	1	-	-	-	-	-	-	-	-		4 (5)
Merck Scharp &Dohme	2	1	-	-	-	-	-	-	-	-	-	-		3 (4)
Gynuity Health Projects	1	-	1	-	1	-	-	-	-	-	-	-		3 (4)
University of Concepcion (Chile)	-	-	-	-	1	-	-	-	-	-	-	2	-	3 (4)
Melinta Therapeutics, Inc.	-	-	1	-	-	-	-	-	-	-	1	-		2 (3)
Eli Lilly	-	1	1	-	-	-	-	-	-	-	-	-		2 (3)
Novartis	-	-	-	-	1	-	-	-	1	-	-	-		2 (3)
PHRI (Canada)	-	-	-	-	-	-	-	1	-	-	1	-		2 (3)
Other pharmaceutical companies	1	1	1	3	1	2	2	1	-	-	2	-	1	15 (20)
Other international institutions	-	-	-	-	1	1	-	2	-	2	1	3	2	12 (16)
Other national institutions	-	-	-	-	1	1	-	-	-	-	1	1	1	5 (7)
Total	6	6	8	4	8	5	3	4	2	5	6	7	11	75

IECED: Instituto Ecuatoriano de Enfermedades Digestivas; PHRI: Population Health Research Institute

Table 3: The proportion of clinical trials registered between 2010–2022 that studied each of the seven disease groups at level 1 and 2 of aggregation and proportion of disease burden

Disease group	% Disease burden	% Clinical Trials	% Gap	Aggregation level
NCD (not neoplasm)	58.5	43.0	26.4^{+}	1
Lesions	16.0	1.0	93.8*	1
CD, maternal, neonatal, and nutritional diseases.	14.5	34.0	0.0	1
Cancer total	10.0	22.0	0.0	1
Total burden by hepatitis B (VHB)	0.3	0.0	100*	1
Total burden by hepatitis C (VHC)	0.3	0.0	100*	1
Total non-alcoholic fatty liver disease burden	0.4	0.0	100*	1
Cardiovascular diseases	10.0	7.0	30.0^{+}	2
Neoplasm	10.0	22.0	0.0	2
Other NCD	8.0	3.0	62.5*	2
Diabetes and kidney disease	8.0	1.0	87.5*	2
Mental disorders	7.0	5.0	28.6^{+}	2
Musculoskeletal disorders	6.0	12.0	0.0	2
Neonatal and maternal disorders	6.0	7.0	0.0	2
Transportation injuries	6.0	0.0	100*	2
Neurological disorders	5.0	1.0	80.0*	2
Unintentional injuries	5.0	1.0	80.0*	2
Digestive disorders	5.0	9.0	0.0	2
Self-inflicted injuries and interpersonal violence	5.0	0.0	100*	2
Respiratory infections and tuberculosis	5.0	12.0	0.0	2
Sensory organs diseases	3.0	0.0	100*	2
Skin and subcutaneous tissue diseases	2.0	3.0	0.0	2
Chronic respiratory diseases	2.0	3.0	0.0	2
HIV/AIDS and STD	2.0	4.0	0.0	2
Other CD	1.0	0.0	100*	2
Substance abuse disorders	1.0	0.0	100*	2
Intestinal infections	1.0	3.0	0.0	2
Nutritional deficiencies	1.0	5.0	0.0	2
Neglected tropical diseases and malaria	1.0	3.0	0.0	2

CD=communicable diseases, NCD=non-communicable diseases. *Total gap/$^{+}$Partial gap

Ensuring that clinical trials, especially in countries like Ecuador, are designed to address prevailing health challenges is imperative. By emphasizing research on diseases that constitute a significant portion of the local disease burden, such as the leading cancers, primary care practices can be informed and improved to detect, manage, and possibly prevent these diseases more effectively. Integrating research insights into primary care strategies allows healthcare systems to enhance outcomes across populations, demonstrating the value and necessity of research that prioritizes and reflects specific community health priorities.

Table 4: The proportion of CTs sponsored by the industry registered between 2010-2022 that studied each of the 22 disease groups at level 2 of aggregation and proportion of disease burden

Disease group	% Disease burden	% Industry CT	% Gap
Cardiovascular diseases	10.0	26.0	0.0
Neoplasm	10.0	18.0	0.0
Other NCD	8.0	0.0	100 *
Diabetes and kidney disease	8.0	20.0	0.0
Mental disorders	7.0	0.0	100 *
Musculoskeletal disorders	6.0	12.0	0.0
Neonatal and maternal disorders	6.0	0.0	100 *
Transportation injuries	6.0	0.0	100 *
Neurological disorders	5.0	0.0	100 *
Unintentional injuries	5.0	3.0	40
Digestive disorders	5.0	0.0	100 *
Self-inflicted injuries and interpersonal violence	5.0	0.0	100 *
Respiratory infections and tuberculosis	5.0	9.0	0.0
Sensory organs diseases	3.0	0.0	100 *
Skin and subcutaneous tissue diseases	2.0	0.0	100 *
Chronic respiratory diseases	2.0	3.0	0.0
HIV/AIDS and STD	2.0	6.0	0.0
Other CD	1.0	0.0	100 *
Substance abuse disorders	1.0	0.0	100 *
Intestinal infections	1.0	0.0	100 *
Nutritional deficiencies	1.0	0.0	100 *
Neglected tropical diseases and malaria	1.0	3.0	0.0

CD=communicable diseases, NCD=non-communicable diseases. *Total gap/⁺Partial gap

In Ecuador, there is a marked research gap in common pathologies such as diabetes, renal diseases, neurological diseases, and even injuries, conditions that, despite having been considered priorities for health research, have not been correlated with research efforts in CT.[24] However, we must assume that, as of 2020, the emergence of severe acute respiratory syndrome coronavirus 2 (SARS-COV2) has changed the global disease burden. Unfortunately, this could not be addressed in this study, as there is no official data regarding the magnitude of the change; however, the research gap should be similar to that reported in this study.

Due to the high costs involved in running a CT, it is essential to describe the impact of pharmaceutical sponsors on them. Thus, Atal *et al*.[7] reported that during the 2006–2013 period, the industry-sponsored an average of 75.1% of CT in South America and 71.2% in Ecuador, being one of the countries with the lowest pharmaceutical sponsorship in the region.[7,24-27] Our study found that 47% of the CT had pharmaceutical sponsorship, a difference that could be due to the different time periods analyzed.

The industry's economic contribution in middle and low-income countries helps to strengthen health systems, increases research capacity, and allows extrapolation of CT results; however, it increases the risk that the production of knowledge is directed to market forces, leaving aside the most relevant health problems for these countries.[28] In 1997, the Global Forum for Health Research adopted the term "10/90 gap" and highlighted that somebody put less than 10% of worldwide resources devoted to research were put towards health in developing countries, where over 90% of all preventable deaths worldwide occurred.[29,30] In our study, we can see that, although the pharmaceutical industry covers the needs in the areas of cardiovascular diseases, neoplasms, diabetes, and renal disease, at a general level, it presents more deficiencies when compared with the total number of performed CTs (63.6% vs. 50.0%).

Our study presents significant limitations. The data from the registries are self-reported, so the integrity of the information entered from each CT cannot be determined. On the other hand, there could be discrepancies between the declared CT locations and the locations that enrolled patients, as well as the existence of CT performed without notification or report: only 24 of the 75 CTs identified were found in the ARCSA (national) registry, which demonstrates the lack of follow-up and knowledge of the current regulations.[31] Clinical trial reporting is essential to verify compliance with good clinical practices and bioethical principles[32] and to monitor international rules,[33] which requires a more in-depth analysis that is not part of the objective of this study.

Conclusion

In Ecuador, despite the increase in everyday spending on health from 6.1% in 2010 to 7.8% in 2019[34] and the slight increase in research and development spending from 0.4% in 2010 to 0.44% in 2014 (last report),[35] production related to CTs has been undermined. The overall analysis shows that scientific low

output developed in Ecuador is not adequately correlated to the pathologies with the most significant burden, leaving aside frequent and severe diseases such as diabetes, renal diseases, and chronic non-communicable diseases (hypertension, dyslipidemias, among others), demonstrating the need to increase the development of CT directed towards the study of these conditions through the generation and promotion of external or internal investment.

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Conflicts of interest

There are no conflicts of interest.

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