Ethiopian Medical Journal 2025, 63(supplement 1)
Open access articles distributed in terms of
Creative Commons Attribution Licence [CC by 4.0]
ISSN 0014-1755 eISSN 2415-2420
Maru et al

Original Article

Regulatory System Opportunities and Barriers for Conducting Clinical Trials in Ethiopia: A Descriptive Qualitative Study

Mehiret Maru[1], Eyasu Makonnen[1, 3] ,Yimtubezinash Woldeamanuel[*1, 2]

[1] Center for Innovative Drug Development for Africa (CDT Africa), College of Health Science, Addis Ababa University, Ethiopia
[2]Department of Microbiology, Immunology and Parasitology, College of Health Science, Addis Ababa University, Ethiopia
[*]Corresponding Author
[3]Department of Pharmacology and Clinical Pharmacology, College of Health Science, Addis Ababa University, Ethiopia

*Corresponding author: yimtuwa@gmail.com

Abstract

Background*: Most clinical trials have been conducted in developed countries, and out of the total 343, 835 trials conducted worldwide only 157, i.e., 0.047% have been conducted in Ethiopia as of 26 June 2020. Ethics and regulatory review systems have been stated as the second most common barrier to trial development in Africa. All clinical trials to be conducted in Ethiopia have to get authorization from the Ethiopian Food and Drug Authority (EFDA). However, no study has been done to investigate the effects of clinical trial regulation on clinical trial development in Ethiopia. In this study, we sought to study the enablers and barriers of the regulatory system for the conduct of clinical trials in Ethiopia.*

Method*: A descriptive qualitative study was done from January 01, 2020 – April 25, 2020. Thirteen clinical trial investigators and 2 staff working in the clinical trial team of EFDA were interviewed. The data were analyzed in a thematic way of analysis.*

Results*: the establishment of a team in EFDA with a guideline and committed staff responsible for clinical trials regulation were opportunities; while inadequate staff, financial constraints, space shortage, lack of trial site follow-up inspection, absence of timely feedback to reports, and lengthy approval process were identified as barriers for the development of clinical trials in Ethiopia.*

Conclusion: *In Ethiopia, clinical trial researchers face substantial ups and downs starting from clinical trial authorization to completion. Though the regulatory body is trying to facilitate clinical trial authorization and regulation, the system needs improvement by building and/or strengthening regulatory capacity to encourage investigators to conduct clinical trials in Ethiopia.*

Keywords*: Clinical Trial, Ethiopian Food and Drug Authority, Opportunities, challenges, regulatory system*
Citation : *Maru M, Makonnen E, Woldeamanuel Y. Regulatory System Opportunities and Barriers for Conducting Clinical Trials in Ethiopia: A Descriptive Qualitative Study. Ethiop Med J 63 (supplement 1) 33– 45*
Submission date : *19 November 2024 Accepted: 29 May 2025 Published: 1 June 2025*

Introduction

A clinical trial is a study conducted with human participants to search for new interventions for the promotion of public health (1,2). Data generated from clinical trials help to add medical knowledge, make healthcare decisions, and revise and/or develop treatment guidelines. They also provide information on treatments' cost-effectiveness, the clinical value of a diagnostic test, and how treatment improves the improvement of quality of life (3).

Clinical trials were largely restricted to industrialized nations with only a limited number of clinical trials conducted in developing countries. The involvement of

developing countries has shown an increase over the past few years (1). The African continent offers conducive environments for implementing clinical trials, such as minimal costs for implementation, diverse populations, varieties of diseases, and populations who may not have been previously exposed to any kind of modern medicines (4). Despite these advantages, the number of clinical trials conducted in African countries is still a small proportion compared to those conducted in other parts of the world. According to the clinicaltrials.gov database, among the 343,835 trials done worldwide up to June 26, 2020, only 10,249 (2.98%) have been conducted in Africa; of which the share of Ethiopia is only 1.53%, compared to Egypt (41.93%) and South Africa (27.24%) (5).

Different factors have been identified as barriers that forced Africa to contribute a few clinical trials to the world. Such barriers included a lack of expertise, budget, infrastructure, and conducive research environment, as well as ethical/regulatory challenges, language/culture barriers, and socio-political conditions (2,6-14,15,16). As there are several stakeholders involved in clinical trials, it is important to understand the role of each stakeholder in the development of clinical trials. Out of these stakeholders, Ethiopian Food and Drug Authority (EFDA) is a governmental institution that is legally mandated to regulate clinical trials which are conducted in Ethiopia. In the Ethiopian Food and Medicine Administration Proclamation No. 1112/2019, the role of EFDA and different legal issues in clinical trials are clearly stated in article 27, sub article 1-11 (17). The main role of EFDA is Authorization of clinical trials and to conduct periodic GCP inspection. While some trial investigators have expressed concerns that the lengthy regulatory approval process may contribute to a decline in interest in conducting clinical trials in Ethiopia, there is a lack of empirical evidence to support this perception. To date, no comprehensive study has been conducted to explore the potential challenges and opportunities within the existing regulatory system that may influence the implementation of clinical trials in the country. Therefore, this study aims to examine the regulatory environment in Ethiopia to identify both facilitators and barriers that may require improvement.

Method

Study Design, Area, and Period

The study employed descriptive qualitative design. Data were gathered from investigators with clinical trial experience across hospitals, universities, and dedicated clinical trial sites in Ethiopia. Previously conducted and ongoing clinical trials in universities, hospitals, and research institutes were identified through the EFDA database, https://ClinicalTrials.gov and http://apps.who.int/trialsearch/default.aspx. The top six trial sites were selected as study areas based on the level of their involvement. The selected study areas were the College of Health Sciences, Addis Ababa University (AAU); All Africa Leprosy Rehabilitation &Training (ALERT) Hospital (Addis Ababa); Jimma University Referral Hospital (Jimma); Gondar University Hospital (Gondar); Hawassa Hospital (Hawassa) and Arba Minch University (Arba Minch). Data were collected from January 01, 2020 – April 25, 2020, by the principal investigator of this study.

Study Participants

Clinical trial investigators and members of the EFDA clinical trial team took part in this study. The study involved EFDA-authorized clinical trial investigators from selected regions who had previously served as a Principal Investigator (PI), Co-Principal Investigator (Co-PI), or coordinator at least once, were present during data collection, and provided informed consent. Those who were involved in behavioral trials were excluded from this study as these did not require trial authorization from EFDA. EFDA staff who were working in the clinical trial unit of EFDA with experience in clinical trial regulations, who were available at the EFDA office during data collection and who gave informed consent to participate in the study were also included in this study. Criterion and snowball sampling methods were used, and 18 individuals were invited to participate in this study. Out of these 15 individuals (13 trial investigators and 2 EFDA clinical trial team staff) met eligibility criteria and participated in the study, while 2 trial investigators and one EFDA staff were not able to take part in the study because they were not available during the data collection period. As there is no general agreement on sample size determination for qualitative studies, the sample size was determined by theoretical saturation for this study.

Data Collection

A semi-structured interview guide was prepared in English and translated into Amharic. The guide was pretested, and all necessary corrections were made. The interviews were conducted at places convenient to participants and interviews were all conducted in person. An in-depth interview was conducted by the main researcher and the first two interviews were in Amharic; however, the remaining interviews were conducted in English realizing that English was the working language for the respondents. The interview took 36 – 92 min and was audio recorded with the permission of the respondents. Ethical approval was obtained from the Scientific and Ethics Review Committee of the Center for Innovative Drug Development and Therapeutic Trials for Africa (CDT Africa), CHS, AAU. Informed consent was obtained from each participant before starting the interview. Both the voice and the transcribed data were kept on a computer locked with a password

Analysis

The recorded interviews were transcribed to a Word file and information was anonymized to assure confidentiality. The Amharic transcriptions were translated to English and a neutral person was consulted to validate the translation. The transcriptions were read repeatedly to become familiar with the data, and a thematic data analysis method was implemented. The thematic analysis was approached in an inductive way of coding. The first 4 transcribed data were imported to open code version 4.03, then coded by the main researcher and another person independently. The two individuals discussed the codes and the code list was prepared. A codebook was developed after 4 transcriptions were coded based on the listed codes, the mutual exclusiveness of each code was checked and minor changes were made to the codes. The remaining data were coded and the newly emerged codes were included in the codebook. The identified codes were grouped into sub-themes, themes, and categories.

Result

Thirteen trial investigators and 2 EFDA staff working in the clinical trial team participated in this study. The respondents were 2 females and 13 males. Most of the investigators have a Ph.D. and clinical trial experience of 16-20 years (Table 1). Amongst these, 13 were PIs, nine co-PIs, one investigator and 4 were in other areas of responsibility (Monitor and DSMB member and chairperson; Coordinator; Supervisor; Collaborator)

Table 1: study participants characteristics

Highest Academic level (n=15)		**Engagement in clinical trials (n=15)**		**Number of trials being involved (n=13)**	
MD	2	1-5 years	3	1-3	5
BSc	2	6-10 years	8	4-6	6
MSc	1	11-15 years	3	7-9	1
PhD	10	16-20 years	1	10-12	1

Clinical Trial Approval Procedure

Trials to be conducted in humans on products including drugs, vaccines, diagnostics, food supplements, herbal products, and other biological products, as well as bioequivalence/bioavailability are required to have ethical review and approval by ethical review committees at various levels before getting authorization by EFDA. After approval is obtained from EFDA the trial can start in compliance with GCP standards (18). Parallel submission to EFDA and the National Health Research Ethics Review Committee (NHRERC) has been introduced during the COVID-19 Pandemic, to facilitate the process.

The findings of this study showed that the clinical trial team from the Product Safety Directorate of the EFDA would be responsible for all issues related to clinical trials. To obtain EFDA authorization an investigator would need to submit the trial protocol together with all related documents both in hard and soft copies, plus ethical approval from respective institutional review boards/ethics committees and ethical approval with the NHRERC approval letter if already obtained. In addition, the receipt of service fee payment had to be sub mitted to the directorate, which is a prerequisite to start the review process. The process is shown in Figure 1.

The EFDA guideline does not indicate a clear timeline for clinical trial authorization (18); though it had been stated in the Citizen charter that the review process would take 6 days to give the first response. However, according to the response given by the staff of EFDA who works at the clinical trial team, it was also noted that the review duration depended on completeness of the submitted document, trial complexity, level of risk to participants, phase of the trial, number of protocols submitted within the same period, presence of other prioritized staff responsibility, number of staff in the team, investigator's timely response the review feedback and communication between the investigator and regulatory staff. The longest time taken to review and provide the first feedback for a low and high risk trials were 1 month and 2- 3 months, respectively. It was also observed that it might take 2-4 months to give trial authorization.

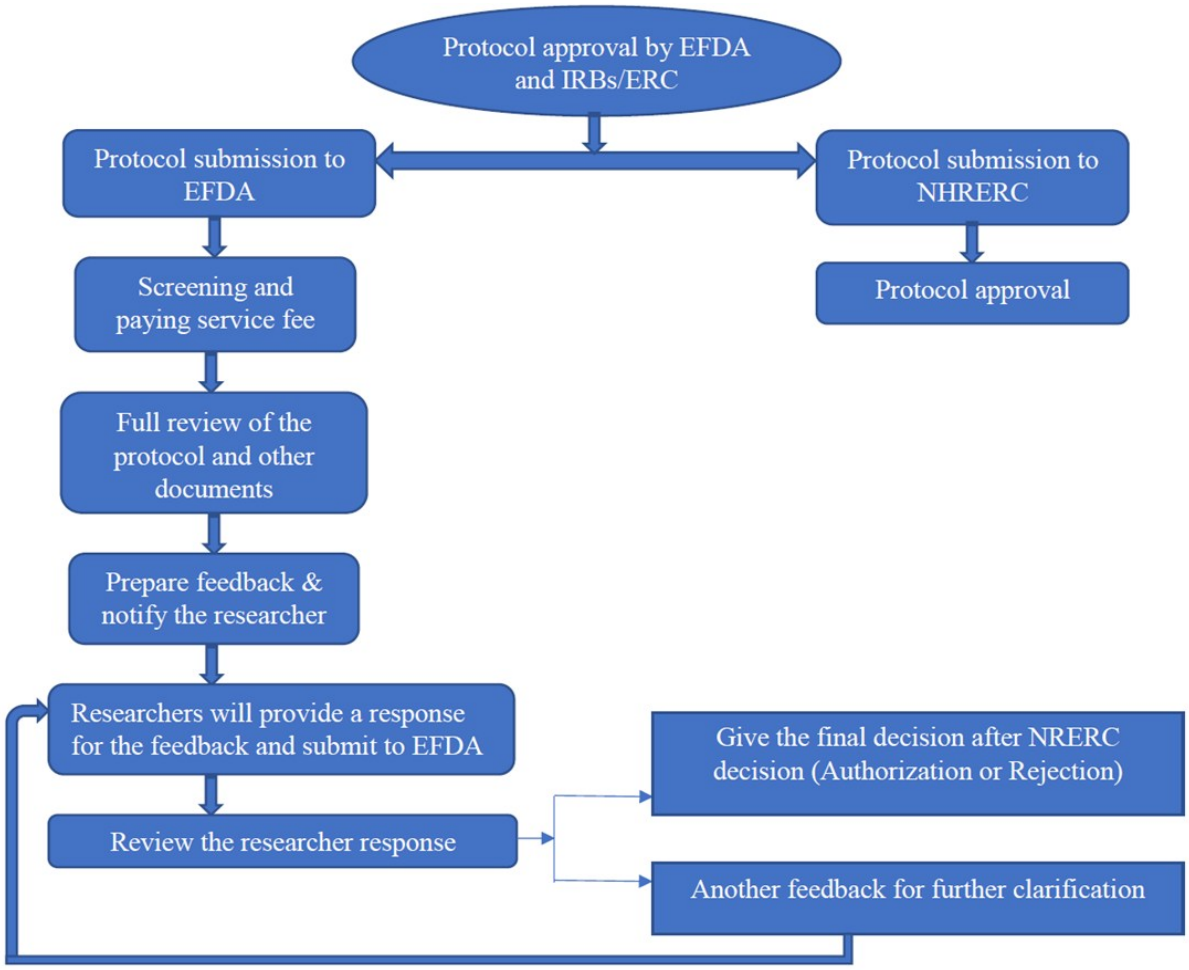

Figure 1. Clinical trial authorization process at EFDA

The EFDA website and workshops organized by the authority and other stakeholders were used to introduce EFDA's roles and responsibilities and to avail various guidelines for the public. The trial team of EFDA had its email in addition to personal work email used for Serious Adverse Effect (SAE) reporting, feedback/information exchanges, and to communicate any trial-related issues.

Mandates of EFDA on clinical trial

The role of EFDA and different legal issues in clinical trials are clearly stated in article 27, sub- articles 1-11 of the Food and Medicine Administration Proclamation No. 1112/2019 (19); (19). The Ethiopian Food and Drug Authority (EFDA) holds key regulatory mandates throughout the lifecycle of clinical trials, including pre-initiation, implementation, and closeout phases. Prior to trial commencement, EFDA is responsible for protocol authorization and site visits. During implementation, it conducts site inspections, reviews periodic and serious adverse event (SAE) reports, provides feedback, and has the authority to suspend, reinitiate, or terminate trials, as well as issue permits for the import and export of trial materials. At the closeout stage, EFDA performs final site inspections, reviews closeout reports, provides feedback, authorizes the use or publication of trial results, and oversees the disposal of leftover materials.

The findings of this study show that commitment of EFDA's staff and management on the regulation of clinical trials was considered to be an opportunity. The staff's motivation to learn, improve their capacity, do routine activity, provide service, participate in joint meeting with research institutions and communicate during trial inspection were also some of the opportunities mentioned. The commit-

ment of the management to address staff capacity building by giving chance for graduate studies and short-term training; having country-specific trial authorization and inspection guidelines; making trial authorization and GCP guidelines accessible online; permitting parallel submission of trial applications to NHRERC were also mentioned as opportunities by investigators.

The EFDA staff highlighted the authority's initiative to address payment-related issues and restructure the clinical trial team as a key opportunity. Additionally, staff participation in national and international conferences and workshops, along with access to a dedicated office and reliable internet, were recognized as valuable factors contributing to improved trial regulation. Three of the investigators, however, did not agree with the aforementioned opportunities, as one respondent stated

"No, no opportunity at all" RSOB GU001.

Strength of the regulatory system

The strengths of the regulatory system stated by the respondents were the presence of EFDA to regulate clinical trials; safeguarding trial participants from unethical practice; doing in-depth protocol review; and online application for trial material importation as one respondent said

> *"… so the good thing is just we have the structure, the institutions, the mechanisms … that is the strength by itself." RSOB JU003*

Two investigators mentioned that EFDA being the only stakeholder responsible for GCP inspection could be considered a strength of the regulatory system, while another investigator expressed confidence in the system, and said

> *"I always have confidence in what EFDA does if the EFDA approves a clinical trial, that clinical trial would have had appropriate scrutiny. The drugs would have had appropriate evaluation or assessment."*

Another perceived strength of the regulatory system both by researchers and EFDA staff was the existence of nationally recognized and legally binding proclamation for trial regulation and GCP guidelines which could help guide researchers on how to conduct a trial in the country.

The presence of a clinical trial team within EFDA responsible for trial regulation, the staff's upfront communication during the site inspection, and the progress made through time were also mentioned as another strength.

One respondent believed that providing trial authorization within a short period is a strength of the regulatory system by saying

> *"Maybe I am lucky …., the time we spent for approval was far from what I expected and I see this strength."*

Three investigators were unable to identify any strengths or positive aspects of EFDA's clinical trial regulation system. And one respondent expressed this by saying

> *"It was mostly difficult and it's hard to think of some good things…… there weren't any good things" RSOBC003.*

Challenges of the Regulatory System

Under this theme, respondents highlighted challenges related to both resources and the system. Poor staff profile of the clinical trial team, limited financial resources, weak infrastructure, and unsuitable working documents were some of the identified resource-related challenges at the time of data collection (January 01, 2020 – April 25, 2020).

Challenges related to human resource

Although some researchers lacked precise data on the clinical trial unit's staffing, they noted from experience that an insufficient number of staff to support trial-related services and the lack of delegation in their absence posed significant barriers to clinical trial implementation by stating that

> *"I think the challenge is they don't have enough staffing so if that person is on meeting your issue will be suspended…" RSOBC001. The lack of adequate number of staff was also mentioned as a challenge by EFDA staffs.*

In association with staff's capacity: At the time of data collection (January 01, 2020 – April 25, 2020); limited training on clinical trials, lack of capacity and experience to review protocols and to regulate clinical trials were mentioned as a challenge by most of the researchers. In addition to this, some of the researchers mentioned that: most staff have first degrees only, not being able to understand researchers, and do not have practical experience in trial implementation a challenging factor in conducting clinical trials in Ethiopia. As one of the respondents mentioned there was also a language barrier and a lack of capacity to write review feedback and site

visit reports as well as a lack of understanding and experience in some types of clinical trials which hindered trial development. The concern about the lack of training in trial-related issues was also shared by EFDA staff.

Limited professional mix within the trial regulation team such as not having physicians, not having a committee to do protocol review, having double responsibility, and being busy with other activities like going to the field with multiple activities, attending meetings, and not being in the office to do the review and to meet investigators were mentioned as barriers by clinical trial researchers. Staff having dual or other prior responsibilities, and lack of professional mix were also mentioned by the EFDA staff as factors that contributed to inefficient trial regulation.

Additionally, staff turnover often due to individuals gaining experience in clinical trial regulation or pursuing further academic qualifications was identified by several researchers as a barrier to trial development. Furthermore, three investigators from other regions reported significant difficulty accessing staff at relevant offices, which resulted in considerable inconvenience, including time delays and financial burdens during their stay in Addis Ababa. Some more barriers such as poor understanding of the importance of clinical trials; not realizing that regulating clinical trials was their duty but rather assuming the staff was doing a favor to the investigators; misunderstanding the current global situation of clinical trials and not considering the country' and global need of medical innovation, and misunderstanding as if the trial benefits only investigators were mentioned by some respondents. One of the researchers endorsed this point by saying

> *"... for EFDA staff, a clinical trial is beneficial only for PIs but not for the country…"RSOBC001*

Three respondents indicated that though the proclamation allowed the involvement of vulnerable groups in clinical trials with justification, the staff tended to reject all trials involving vulnerable populations; and one respondent said the automatic rejection of trials on vulnerable groups without even writing a letter to explain the reason for the rejection could be a barrier to conduct such types of trials in the country.

Difficulty to identify a responsible office or proper direction of whom to contact, during the first visit to submit an application were mentioned as challenges for the new investigators. Even for more senior investigators, as was mentioned by three of the respondents, the frequent change of the staff and office location within the authority and difficulty in identifying the right person for specific issues were also considered to be challenges.

Six of the respondents mentioned that they did not have information about the number of staff, their profession, level of education, and trial reviewing experience.

Challenges related to financial and infrastructure resource

During the time of data collection (January 01, 2020 – April 25, 2020); challenges related to financial resources mentioned by EFDA staff included a lack of budget to organize or attend trial-related training organized by other stakeholders; having only insufficient governmental budget for trial regulation; and lack of support from partners of EFDA who were working in other units of the regulatory body. The absence of a laboratory equipped to test the quality of imported products for clinical trials was identified as a barrier to trial implementation. Additionally, one staff member highlighted infrastructure-related challenges, including insufficient secure and dedicated space for archival purposes, as well as an inadequate office setup.

Challenges related with criteria and guidelines

Criteria:

Having the same criteria for all types of trials and not contextualized requirements with the country's situation and with the type of product to be investigated were mentioned by 5 respondents as barriers to conducting trials on some areas of national need and traditional medicine. As one of the respondents mentioned, having the same criteria for trials conducted by university students as partial fulfillment of their training and trials conducted on new drugs were barriers to encouraging new investigators to conduct clinical trials. One of the investigators mentioned that some criteria were included only for the sake of completing the form leading to extra pressure on investigators rather than protecting trial participants.

However, seven respondents involved mainly in clinical trials funded by international funding organizations responded that there were no unnecessary criteria requested for trial authorization. Some criteria considered unnecessary and difficult to fulfill are described in Table 2.

Table 2: Criteria considered unnecessary and difficult to fulfill

	Criteria	Number of respondents
Difficult to Fulfill	Insurance coverage especially for locally sponsored trials	2
	Manufacturer's credential	1
	For traditional medicine Preparation of investigator brochure, dossier	1
	Good Manufacturing Practice certificate for laboratory-scale production of Ips	1
Unnecessary	Produce data about previous studies in Ethiopia	1
	A pre-requisite to be a PI needs to work as Co-PI	1
	For multi-country trials pre-requiring other countries' Approval	2

Guidelines:

Concerning clinical trial authorization guidelines, many barriers were raised both from the researchers and the regulatory staff which hindered trial development and implementation. The most commonly mentioned challenges by 6 of the respondents were lack of detailed information on the guidelines with specifications for the involvement of vulnerable groups in research, not having clear procedure about the process of trials authorization, and not stating the timetable for each activity undertaken in the review process were stated as a barrier for most of the researchers. One respondent mentioned that the time frame should be stated for each activity;

> *"When should you expect your comments? When should you respond? Within what period you should respond to those comments. And after you submit your comment when do you expect the approval? Those things should be kept clear." RSO-BAH003*

Some challenging factors were shared by both the regulatory experts and researchers. Having impractical guidelines and not having Standard Operating Procedures (SOP) for protocol review were mentioned as barriers by one investigator and an EFDA staff. As few of the respondents mentioned, using the same guidelines for different types and phases of trials like trials on traditional medicine and modern medicine is a barrier to doing clinical trials in Ethiopia.

One of the researchers mentioned the nature of the guideline will lead the EFDA experts to make a personal decision, and another researcher stated lack of detailed information about specific issues on the guideline is a barrier. Lack of specific guidelines for trial materials importation, taking ample time to revise and apply regulation, and not regularly updating the guidelines were also considered barriers by different researchers.

System-related challenges

System-related challenges associated with trial authorization, service fee, product import/export, follow-up inspection, report and feedback provision, product disposal, means of communication, and overall trial regulation system were discussed under this theme.

Challenges related to authorization

Except for three of the respondents, others described the prolonged trial review/approval process as a challenging factor for trial development. The approval process took 2 months up to 2 years as reported by investigators. EFDA staff indicated that the first review response might take 1 to 4 months, while the query response1-4 weeks. One respondent stated that in the case of a multi-country trial, by the time the trial got approval by EFDA, recruitment was completed in other countries.

Few respondents mentioned irrelevant detailed review comments and contradictory comments given by different individuals as barriers. Not having a clear platform for the approval process was also mentioned as a challenge by limited respondents. Requiring hard copy submission of documents and a poor archiving system for trial-related documents were also barriers. Other challenges mentioned for trial authorization were reviewing protocols in a way of faultfinding; not having a joint review system with ethics committees; not involving external reviewers and lack of a system to consult experts in the protocol review process were mentioned by few of the respondents.

Not having a clear guide on where to go and how to apply and no protocol prescreening during submission were pointed as challenges by two of the researchers. One of the respondents reported that not providing a letter of receipt of the application mentioning the date and number of documents submitted made the review follow-up difficult.

The lack of a streamlined approach for amendment was stated as a challenge by one of the researchers, while another researcher mentioned the lack of clear guidelines for approval or rejection of trials as a challenge. The absence of a system to handle researcher complaints and the lack of a system for notifying investigators upon review completion were stated as challenges by some of the researchers.

Challenges related to service fee

More than half of the respondents stated, that not making a distinction between self-initiated or locally sponsored trials from external or industry-sponsored trials, charging the same amount for all trials, and requesting fees to be paid in dollars both for authorization and protocol amendment as barriers that hinder the involvement of national researchers in clinical trials and trial development in Ethiopia.

The amount of the service fee is excess even for sponsors and for self-initiated and/or locally funded trials was stated as a challenging factor by some of the researchers. However, eight of the respondents felt that the fee was fair and reasonable for trials funded by industries or pharmaceutical companies. Bureaucratic and time-consuming payment process which delayed approval and hindered trial implementation was also identified as barriers by half of the researchers. One of the respondents described the amendments fee by saying

" *the number of amendments should be determined by what is needed scientifically not what can be afforded by the project. Otherwise, you know that is a real danger for doing unsafe practice "* RSOBC003

As described by a few researchers, not posting the requirement of service fee and its amount on EFDA's website, paying service charge being a pre-requisite for protocol review, not getting good service compared to the amount paid, deciding service charge related issues without consulting other stakeholders and unwillingness of sponsors to pay this much are existing barriers which affect trial development in Ethiopia. On the contrary, one of the EFDA staff mentioned that the service fee was reasonable compared to that of other countries and the regulatory services given. One of the respondents did not have any information about the service charge.

The regulatory staff also stated not posting on the website and including in the guidelines the updated issues regarding service fees like the possibility of paying in birr for nationally sponsored trials created an information gap.

Challenges related to trial materials import/ export

Though the online product import application system was commendable, the delay in getting product import permission from EFDA and difficulty in following the application progress were mentioned as barriers, not having a complaint handling system for issues related to the online application was also mentioned as a challenge while some researchers in the regions stated in- person application for sample export permit and time taking to obtain the permit were also barriers which cause loss of money and time.

Time taking paperwork at customs, not getting 24-hour service from EFDA at the airport, and delayed product inspection at the port of entry were pointed out to be challenges. EFDA staff working at the port of entry, lacking knowledge about Investigational Products (IPs) was also identified as a challenge by one researcher. As most of the researchers stated, not giving one an export permit for all trial samples to be shipped and requiring one to apply each time makes the sample exportation process much challenging; and the need to apply for import of the same IP each time was stated as barriers by one of the researcher. Also, few researchers point out frequent changing import requirements as a barrier to IP importation.

Not having a separate custom system for trial-related materials import and export, lack of infrastructure to maintain product storage condition at custom, zero level flexibility on custom requirements were also mentioned as challenges

Challenges related to site inspection
The majority mentioned the lack of regular site inspection and follow-up as a barrier while only one of the respondents mentioned that there was regular site inspection from EFDA.

Not being inspected timely, doing only checklist-based inspection, not doing further investigation, not providing onsite support to investigators, and inspecting for fault-finding were pointed out as a challenge.

According to the staff of EFDA, not doing site inspections as planned and not having Standard Operating Procedure (SOP) to prioritize trials for conducting site inspections were also stated as a gap.

Challenges related to report and feedback
Lack of initiative to request investigators/sponsors for reports, not acknowledging the receipt of reports as soon as received from investigators/sponsors, not giving exact/ clear responses about the progress of protocol review, and not giving timely feedback for requests by investigators/sponsors, were stated as challenges related to report and feedback (N=2).

Challenges related to materials disposal
Respondents highlighted several challenges related to materials disposal, including the lengthy process of IP destruction (N=3), the absence of a separate disposal system for trial products, and delays in issuing disposal certificates after disposal (N=2). Additional concerns included the lack of EFDA-licensed drug disposal companies in the country (N=3), the absence of a structured system for drug disposal applications, and difficulties in identifying the responsible directorate for drug disposal.:

> *"They will not come even after repeated application. They don't even consider drug disposal as their responsibility so you have to beg for this also, write a letter, and later there are also issues to get a disposal certificate."* RSOBC001

In contrast, two of the researchers stated that the disposal process was facilitated.

Challenges related to communication
Regarding communication between the researcher and EFDA staff, there are different factors mentioned as a challenge by many of the respondents. For the researchers coming from other regions in the country; personal visits to the office to have clear and up-to-date information; not having electronic means of authorization application; lack of communication via email; and requiring hard copy submission of protocol and periodic reports are challenging factors which will cause loss of money and time of the researchers. Also for most of the researchers; some issues from EFDA like not responding to office phones and nonfunctional official email addresses make communication more difficult.

Lack of clear information on the website about where to go, what to do, and when to get responses on trial authorization, no information about changes made to the trial regulation system; no online system to send review feedback and no online tracing system on the progress of protocol review; the need for frequent in-person visit to shorten the review process; and not having information about the mandate of EFDA on clinical trials were stated as communication challenges

Challenges related to trial regulation
As few of the researchers mentioned, having an inflexible/too stringent review system that did not consider situations; not having a system to control trials conducted without regulatory authorization/ not being vigilant to identify unauthorized trials as factors that demotivate researchers to apply for EFDA authorization and to conduct clinical trials legally. One of the researchers supports this concept by saying

> *"So even at the time we were struggling to get the ethical clearance, researchers were doing clinical trial without getting authorization and any ethical clearance in Ethiopia ..."* RSOBJU002

Having a stringent system is not attractive for external sponsors and/or investigators leading to discouraging collaborative research; misconception of the regulatory body as if it is the only stakeholder caring for the safety of trial participants; not having a system to follow trial results implication/not considering the expected benefit of the trial for the country were stated as challenging to conduct clinical trials. Focusing on research done in Addis Ababa/ giving less attention to trials conducted in regions; not attending meetings organized by investigators/other stakeholders; and not participating in trainings organized by sponsors were mentioned by some as factors that hindered trial development in the country

Prioritized Problems
After identifying the challenges, respondents were asked to prioritize the challenging factors based on the impact they might have on trial implementation and development. The participants prioritized the problem based on their personal experience, because of that one factor can be a

primary challenge for some researchers while being secondary or tertiary for others (Table 3)

Table 3: Prioritized challenging factors

Prioritized level	Challenging factors	Number of respondents
Primary challenging factor	Prolonged approval duration	4
	Staff capacity, number, and attitude	3
	Overall approval process	2
	Hierarchical trial approval process	2
	Unscheduled trial review process	1
	Unnecessary detailed review	1
Secondary challenging factor	Lack of timely site inspection	2
	lack of professional mix of the staff	1
	Lack of an attractive regulatory system	1
	Approval duration	1
	Lack of harmonized review system	1
	Lack of supportive inspection	1
	Not consulting external reviewers	1
Tertiary challenging factor	Lack of trial-type-specific payment	1
	Approval duration	1
	Not facilitated trial material importation	1
	Fault finding nature of inspection	1
	Staffs capacity	1
	Lack of facilitated drug disposal system	1

Discussion

The study aimed to assess the regulatory system enablers and barriers influencing clinical trial development and implementation in Ethiopia, based on interviews with clinical trial investigators and EFDA clinical trial team members. Meetings organized by EFDA to have discussions with investigators were considered good opportunities to help raise issues that need improvement on trial regulation and get information on the updated issues. The attempts done by EFDA to do protocol reviews and site inspections have paved the way for a legal way of trial implementation. Availability and online accessibility of some guidelines prepared by EFDA could provide relevant information encouraging investigators to be involved in clinical trials.

The EFDA staff expressed that efforts made in building staff capacity through long and short- term training will boost the interest of staff working in the clinical trial team and minimize staff attrition. The supplementary guidance on the conduct of clinical trials on medicinal products during the COVID-19 pandemic and guidelines on traditional medicine clinical trials developed recently is highly encouraging and shows its commitment to promoting clinical trials in the country.

Investigators from the selected institutions expressed their appreciation for what EFDA is doing and believed that it would be a good opportunity to develop clinical trials. The strengths of the regulatory system that respondents mentioned will, no doubt, contribute to the introduction of several GCP-compliant clinical trials.

Though there are opportunities and strengths of the regulatory system that help develop clinical trials in Ethiopia, several challenges faced from trial pre-initiation to completion have also been mentioned which might threaten clinical trials that are being developed.

If investigators face challenges right from the outset, i.e., at the level of trial authorization, they will lose interest in clinical trials and shift their interest to other areas of research. The lengthy process for trial authorization can frustrate investigators and the number of clinical trials expected will go down. Not making relevant information available will harm clinical trial development in the country. Though EFDA staff claimed for presence of a help desk to provide appropriate information to newcomers most of the investigators did not agree with this claim.

The lack of expertise, training, and experience of staff at EFDA leading to the lengthy review process reported in our study is in agreement with those of the previous studies (1,12). The findings of the present study are also in agreement with those obtained from a similar study done on a review of regulatory oversight of clinical trials in Africa (13), which identified barriers like the limited number of staff with a limited mix of professions within the clinical trial team which called upon a need for academic improvement to affect protocol review process and the final decision made by the regulatory system. The absence of clear criteria for excluding vulnerable groups in trials and the lack of consideration for global experiences were identified as barriers to generating local data tailored to the country's specific needs. A similar study conducted in Ethiopia highlighted comparable challenges in self-initiated trials, particularly the difficulty of involving vulnerable groups in research (11).

The other major factor mentioned as a barrier by almost all researchers was associated with the service fee for trial authorization including protocol amendments such as payment to be effected in dollars and non-discriminatory amounts irrespective of differences in trial types and sponsors. The requirement to pay the service fee for protocol amendment in dollars might force investigators not to apply for every amendment they made leading to the possibility of unethical practice which might harm trial participants.
The absence of specific criteria for different types, natures, and phases of trials in the regulatory guideline hindered the development of traditional medicines through clinical trials. A systematic review similarly reported that the absence of a clear schedule for each activity in the guideline was a barrier to implementing trials as planned by researchers resulting in sponsors' loss of interest in conducting trials in Ethiopia (6).

In agreement with the findings of a previous qualitative study carried out in Ethiopia to investigate barriers and enablers to the implementation of local investigator-initiated clinical trials (11), most investigators in the present study pointed out that the extended time that issuance of a trial authorization takes leads to delayed trial initiation which is a barrier for the involvement of Ethiopia in multi-national, externally funded and international companies sponsored trials because sponsors and funders lose interest to conduct trials in Ethiopia. The stringent review process carried out sequentially at various levels of ethics committees and feedback will discourage investigators from conducting clinical trials. Similar to that of the study that identified difficulties in conducting clinical trials for AIDS-associated Kaposi's sarcoma in SSA (20), our findings also revealed that lack of coordination between ethics committees and regulatory bodies to harmonize trial protocol review process has delayed trial approval resulting in loss of investigators' interest to be engaged in clinical trials.

Product importation for clinical trials was identified as a significant challenge in trial implementation. The lengthy process of securing import permits for investigational products (IPs) and frequent changes in import criteria have resulted in additional costs and wasted time for investigators and sponsors. A review on vaccine trials in Africa also highlighted that delays in obtaining product import permits contributed to budget constraints due to local currency depreciation (8). After having the permit; customs clearance and product inspection at the port of entry by EFDA staff also took longer time. The absence of a temperature-regulated storage area at the port of entry will result in premature decomposition and damage of the imported products before use incurring additional costs and leading to loss of sponsors' interest to work in Ethiopia. That is why most of the trials are conducted in countries with efficient regulatory systems and customs clearance. This means Ethiopia cannot be competitive in attracting external company-sponsored trials.

The requirement of in-person application for material transfer permit for each material at EFDA headquarters can discourage investigators from outside Addis Ababa from conducting clinical trials as this incurs additional cost and time. The absence of a separate custom system for trial

materials importation also discourages researchers from being involved in clinical trials as this also incurs extra expense, inconvenience, and time wastage.

During trial implementation, the absence of a regularly scheduled site inspection will be a barrier to conducting GCP-compliant trials, i.e., participant protection and data credibility will be serious problems. Even in scenarios where site inspections were conducted, they did not achieve the objectives of inspection as the staff had no experience so it focused on faultfinding. Not giving timely feedback and even not acknowledging the receipt of the reports by EFDA to the SAE and progressive reports as mentioned by most respondents will discourage investigators from sending reports in the future, which has an impact on GCP compliance.

There was also an absence or delay in providing feedback for trial closeout reports which could prolong the trial completion period unnecessarily as regulatory approval is a requirement to complete clinical trials. Not getting feedback on time, requiring a long time for the disposal of the leftover investigational products, and not providing a disposal certificate on time were also barriers to completing trial document compilation on time resulting in frustration.

In contrast to the findings of the previous qualitative study done to assess barriers and enablers to locally-led clinical trials (21), the existence of a regulatory body with legally stated roles and responsibilities was considered to be one of the regulatory strengths in our study.

Conclusion

In a country where a limited number of trials are conducted, many qualitative studies designed to identify the enablers and barriers in the conduct of clinical trials may not be expected, but we believe that our descriptive study will contribute to the improvement of the clinical trial regulation system in Ethiopia. The results of our study suggested that not having a strong, and responsive regulatory system will harm clinical trial development in the country. Though there are opportunities for making the regulatory system stronger, the challenges that investigators/sponsors are facing should not be overlooked. These challenges have to be carefully addressed to encourage the conduct of clinical trials in Ethiopia. Further studies have to be done to measure the impact of each challenge on the development of clinical trials, prioritize the impacts, and come up with recommendations that will enable the increase in the number of clinical trials and facilitate their GCP-compliant conduct in the country

Acknowledgment

We would like to thank CDT Africa for technical and financial support and the study participants for taking part in this study.

Declaration of Conflicting Interests

The authors of this study declared that they have no potential conflict of interest.

Funding

This study is funded by CDT-Africa, Addis Ababa University, which is a World Bank supported center of excellence [Grant Id: P151847-IDA57940]. The views expressed in this publication are those of the author(s) and not necessarily those of Addis Ababa University or CDT-Africa.

References

1. Devasenapathy N, Singh K, Prabhakaran D. Conduct of clinical trials in developing countries: A perspective. Curr Opin Cardiol. 2009;24(4):295–300.
2. Chandra RS, Orazem J, Ubben D, Duparc S, Robbins J, Vandenbroucke P. Creative solutions to extraordinary challenges in clinical trials: Methodology of a phase III trial of azithromycin and chloroquine fixed-dose combination in pregnant women in Africa. Malar J. 2013;12(1):1–8.
3. Nichols H. How do clinical trials work and who can participate? Med News Today [Internet]. 2014; Available from: https://www.medicalnewstoday.com/articles/278779#work
4. Nair SC, Ibrahim H, Celentano DD. Clinical trials in the Middle East and North Africa (MENA) Region: Grandstanding or Grandeur? Contemp Clin Trials [Internet]. 2013;36(2):704–10. Available from: http://dx.doi.org/10.1016/j.cct.2013.05.009
5. Definitions DE, Arm AA, Certification C, Condition C, Cross-over CC, Committee DM, et al. Hide glossary.
6. Alemayehu C, Mitchell G, Nikles J. Barriers for conducting clinical trials in developing countries- a systematic review. Int J Equity Health. 2018;17(1):1–11.
7. Kochhar S. Challenges and impact of conducting vaccine trials in Asia and Africa: New Technologies in Emerging Markets, October 16th-18th 2012; World Vaccine Congress, Lyon. Hum Vaccines Immunother. 2013;9(4):924–7.

8. Idoko OT, Kochhar S, Agbenyega TE, Ogutu B, Ota MOC. Review: Impact, challenges, and future projections of vaccine trials in Africa. Am J Trop Med Hyg. 2013;88(3):414–
9. Mbuagbaw L, Thabane L, Ongolo-Zogo P, Lang T. The challenges and opportunities of conducting a clinical trial in a low resource setting: The case of the Cameroon mobile phone SMS (CAMPS) trial, an investigator initiated trial. Trials. 2011;12:1–7.
10. Fekadu A, Teferra S, Hailu A, Gebre-Mariam T, Addissie A, Deressa W, et al. International Clinical Trial Day and clinical trials in Ethiopia and Africa. Trials. 2014;15(1):1–6.
11. Franzen SRP, Chandler C, Enquselassie F, Siribaddana S, Atashili J, Angus B, et al Understanding the investigators: A qualitative study investigating the barriers and enablers to the implementation of local investigator-initiated clinical trials in Ethiopia. BMJ Open. 2013;3(11).
12. Grover S, Xu M, Jhingran A, Mahantshetty U, Chuang L, Small W, et al. Clinical trials in low and middle-income countries — Successes and challenges. Gynecol Oncol Reports [Internet]. 2017;19:5–9. Available from: http://dx.doi.org/10.1016/j.gore.2016.11.007
13. Maïga D, Akanmori BD, Chocarro L. Regulatory oversight of clinical trials in Africa: Progress over the past 5 years. Vaccine. 2009;27(52):7249–52.
14. Brennan MJ, Fruth U, Milstien J, Tiernan R, Nishioka SDA, Chocarro L. Development of new tuberculosis vaccines: A global perspective on regulatory issues. PLoS Med. 2007;4(8):1299–302.
15. Terblanche M, Burgess L. Cardiovascular clinical trials in Africa: opportunities and challenges. SA Hear. 2017;8(2):114–21.
16. Kuepfer I, Burri C. Reflections on clinical research in sub-Saharan Africa. Int J Parasitol. 2009;39(9):947–54.
17. FMAP. Food and Medicince Adminstration Proclamation No 1112/2019. Fed Negarit Gaz. 2019;39:11099–172.
18. FOOD , MEDICINE AND HEALTHCARE ADMINISTRATION AND CONTROL AUTHORITY OF ETHIOPIA Second Edition Addis Ababa , Ethiopia. 2017;(June).
19. Gazette FN. FEDERAL NEGARIT GAZETTE Scanned with CamScanner. 2019;
20. Mitsuyasu R. Challenges for conducting clinical trials for AIDS malignancies in resource-limited settings. Curr Opin Oncol. 2011;23(5):461-2.
21. Franzen SRP, Chandler C, Siribaddana S, Atashili J, Angus B, Lang T. Strategies for developing sustainable health research capacity in low and middle-income countries: A prospective, qualitative study investigating the barriers and enablers to locally led clinical trial conduct in Ethiopia, Cameroon and Sri Lanka. BMJ Open. 2017;7(10):1–16.