ADDIS ABABA UNIVERSITY

COLLEGE OF HEALTH SCIENCES

SCHOOL OF GRADUATE STUDIES

CENTER FOR INNOVATIVE DRUG DEVELOPMENT AND THERAPEUTIC TRIALS FOR AFRICA

CHALLENGES AND STRATEGIES FOR RECRUITMENT AND RETENTION OF PARTICIPANTS IN CLINICAL TRIALS IN ETHIOPIA:

A QUALITATIVE STUDY

BY

LEALEM MINWUYELET WAGAW

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Challenges and Strategies for Recruitment and Retention of Participants in Clinical Trials in Ethiopia: A Qualitative Study

BY

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Contents

Declaration

I declare that this is an original report of my research, has been written by me, and has not been submitted for any previous degree or professional qualification. I am aware of and understand the university's policy on plagiarism, and I confirm that this thesis is my work.

Abbreviations/Acronyms

AAU	Addis Ababa University
AHRI	Armauer Hansen Research Institute
ART	Anti-Retroviral Treatment
CDT-Africa	Center for Innovative Drug Development and Therapeutic Trials for Africa
CHS	College of Health Sciences
CRA	Clinical Research Association
CRO	Clinical Research Organizations
CT	Clinical Trial
GCP	Good Clinical Practice
HIV	Human Immunodeficiency Virus
IDI	In-Depth Interview
IRB	Institutional Review Boards
LRTC	Leishmaniasis Research and Training Center
MMV	Medicine Malaria Venture
PIs	Principal Investigators
P	Physicians
RCTs	Randomised Controlled Trials
TB	Tuberculosis
TC	Trial Coordinator
TP	Trial Participant
TN	Trial Nurse
USAID	U.S. Agency for International Development

List of Figures

List of Tables

Operational Definitions

Challenges: something that requires great effort to change or modify.

Clinical Trial: an investigation or research that involves human subjects, undertaken to assess/evaluate the safety and/or effectiveness of a medical product.

Recruitment: active efforts by investigators to identify subjects who may be suitable for enrollment into a clinical trial. Subjects are selected based on the protocol's inclusion and exclusion criteria during the clinical trial recruitment period.

Retention: activities by the clinical trial team to encourage and support a subject to remain enrolled and participate in the clinical trial.

Strategy: a careful plan or method for achieving a particular goal usually over a long time.

A trial participant: also called the human subject, is a person who participates in human subject research by being the target of observation by researchers.

Abstract

Introduction: Clinical trial is an extensive and demanding process, which takes approximately 10 to 15 years. Clinical trials require the active engagement of human subjects. Recruitment and retention of participants are two major challenges in conducting clinical trials. Poor recruitment and retention of participants in clinical trials can lead to major delays in the development of new products and interventions. This can also cause significant problems in the study validity as they could reduce the statistical power resulting in poor generalizability of the study.

Objective: This study is aimed to identify potential challenges and strategies for enhancing recruitment and retention of participants in clinical trials in Ethiopia.

Method: A qualitative methodology with a phenomenological approach employed. Semi-structured interviews were conducted face to face and through telephone. Interviewees were purposively selected from five candidate study sites which are Armauer Hansen Research Institute, Zewditu Memorial Hospital, University of Gondar, Jimma University, and Addis Ababa University. These sites were chosen primarily because most clinical trials conducted in and potential clinical investigator candidates were employed and affiliated there. Investigators, clinical coordinators, physicians, nurses, and participants involved in clinical trials were the study respondents. The sample size was determined using the criterion of informational redundancy. Of 22 potential respondents approached, 19 consented to the interview. An open-ended topic guide was developed to facilitate in-depth interviews with respondents with sufficient freedom to describe their experiences and perspectives that they deemed relevant to the research questions. Interviews were audio-recorded with consent. Transcriptions were entered into Open Code and coded. Data were analyzed using thematic analysis.

Result: Nine of the respondents (47.4%) were females. Respondents were involved as principal investigators (n=5), trial coordinators (n=7), nurses (n=2), physicians (n=2) and trial participants (n=3). Thematic analysis resulted in a generation of 3 main themes and 10 sub-themes. Clinical trial team factors (communication and system-related), participants' factors (communication and interest related), and study factors (complexity of the study and cost-related) were listed as challenges for recruitment and retention of trial participants. Additionally, four subthemes are mentioned under the three themes as a strategy for recruitment and retention of trial participants, such as promoting clinical trials, improving communication skills, refining the clinical trial setting

system, and having a good estimation of cost. Potential challenges and strategies for recruitment and retention of participants in clinical trials were identified under each sub-themes. Poor communication skills, mistreating participants, and lack of knowledge about existing trials are considered to be clinical trial team factors. Also, misconceptions about the trial, low-level education, lack of social support, and participants' moves around were revealed to be an important challenge among trial participants' factors. Also study factors such as long questionnaires and assessment, stringent eligibility criteria, frequent appointment, and extra, and inconvenient procedures. However, a wide range of strategies was identified such as increasing awareness, choosing an appropriate trial site, provisions of training, reimbursement and compassionate respectful care, and establishing an efficient tracking system may be the most important interventions to improve recruitment and retention of trial participants.

Conclusions: Poor knowledge about research, and complexity of trials were the greatest challenges for low recruitment and retention. Interventions to improve knowledge and provisions of training to the clinical trial team and having compassionate respectful care, providing compensation, increasing awareness in the community are important strategies to consider when designing and planning recruitment and retention plan.

Keywords: Challenges, Strategies, Recruitment, Retention, Clinical trial participants, Qualitative and Ethiopia

1. Introduction

1.1 Background

Recruitment is a dialogue process between an investigator and potential participants before consenting. It comprises the identification of potential participants and giving detailed study information to them, hence generating their interest in the proposed study (1). Retention is the strategy or tactics designed to keep enrolled participants from withdrawing participation and "dropping out"(2).

One of the main aspects of designing any clinical trial is to attain the target sample size (3). However, clinical trials are known to have difficulties related to recruitment, compliance, and retention of participants for the study periods, which may cause early trial closures.

Many clinical trials still face challenges in recruitment and retention. The number of planned recruitment and retention of participants doesn't seem to be achieved; this has implications for statistical power, internal and external validities. Recruitment concerns also have practical and financial impacts, as they can postpone the completion of the research or reduce its timely effect on patient health and wellbeing (6). It is very important to have a good estimate of the sample size, as studies that are either too small or too large may be judged unethical (3).

Without adequate participant retention from the time of study commencement to closeout, the goal of the clinical trial cannot be achieved. Having data for evaluation is dependent on successful participant retention. Participants cannot be retained without enrolled volunteers. Initially screened, then enrolled participants depend on designing a successful participant recruitment strategy. The most important focus on all clinical trials is the recruitment of a potential participant (8).

If the dropout rate is more than 20% during trial follow up it can introduce bias, reduces statistical power consequently affects generalizability, scientific validity, and reliability of the study results (9). Therefore, this study scrutinizes challenges and attainable strategies to the success of recruitment and retention of clinical trial participants.

1.2 Statement of the Problem

Clinical trials are high demands of time, resources, investment, and routinely burdensome on participants (4). Clinical trials must recruit and retain the planned number of participants to avoid low statistical power, mainly leading to reporting of clinically significant effects as statistically non-significant. Statistically non-significant findings can increase the risk that possibly effective interventions may be unseen before their true value is recognized or that there will be a delay in proving their value while more trials are carried out (11).

Poor participants' recruitment and retention extend the trial period and can have different pitfalls such as raising ethical problems, mainly when investigators expose participants to interventions with uncertain benefit, inability to determine whether the intervention is clinically effective at the end of the trial, trial period extension and financial impact (12).

Identification of the most important challenges and strategies for recruitment and retention in the design of clinical trials is certainly an important precondition to assess the viability of a trial.

1.3 Significance of the Study

This study has great significance in identifying the potential challenges and strategies for recruitment and retention of participants in clinical trials. Recruitment of participants and retention of the enrolled participants till close out of the trial will decide the accomplishment of clinical trials. Understanding challenges would help improve the recruitment and retention of participants. Addressing the challenges and reviewing strategies will optimize recruitment and retention. Also learning from best practices is very important.

2. Literature Review

2.1 Introduction

This chapter provides narrative reviews of the literature relevant to the study. The key emphasis of the study is on potential challenges and attainable strategies to improve participants' recruitment and retention in a clinical trial. Accordingly, the review looks at the concept of the association among these challenges, and strategies to improve participants' recruitment and retention with clinical trial outcomes suggested by different authors are discussed in this chapter.

The pragmatic approach search strategy for conducting the literature search was adopted. The search was focused on the following most appropriate key search terms: challenges, strategies, recruitment, retention, clinical trial participants' and Ethiopia.

Extensive literature has been written on challenges of recruitment (1, 4,5, 11-22), strategies to enhance recruitment (1, 4,6,11,13-21,23-25), challenges of retention (9,10,15-17,19,21,26) and strategies to improve retention (2,6,9,16,17,19,21,23,26-29)

Usually recruiting a sufficient number of participants to meet the targeted sample size is considered a prerequisite for the successful conduct of clinical trials (27). More often, if patients believe that they will have a chance to have a better treatment or if their contribution can bring a change for future generations; he/she would be keen to give informed consent to be part of in the clinical trial. Still, failing to enroll an adequate number of subjects in a trial is a long-standing problem (16). According to Campbell et al. "one-third of publicly funded trials required a time extension because they failed to meet initial recruitment goal".

Low recruitment and retention of participants in clinical trials are very challenging but common. A previous study showed that the 2579 clinical trials registered in the US National Library of Medicine clinical trial registry which enrolled 48,027 participants and completed in 2011 were unable to answer the primary research questions meaningfully indicating the unsuccessful accrual rate or less than the target sample size (31). As a result, recruitment and retention persist to be a major area of concern for many reasons (16).

An effective recruitment and retention technique comprises clear and comprehensive planning, sufficient resources, regular monitoring, and prompt clarification responses for any problems recognized.

2.2 Recruitment

There are two main goals of recruitment, i.e., to represent the target population and avoid the study from being underpowered (23). Effective recruitment needs enough time to plan, establish community awareness, and make personal contacts (18).

Registering the rate of participants' recruitment in clinical trials is a vital indicator of a clinical trial's progress through time (27). Unable to recruit adequate numbers of participants and fail to meet the study timetable in clinical trials has major negative implications (13, 14). Consequently, the study period might need to be pushed resulting in increased costs and protocol amendments (14).

2.2.1 Recruitment Challenges

The success of clinical trials depends on participants' recruitment, though many recruitment challenges have been recognized (5). There are a lot of factors associated with investigators, participants, protocols, and organizations that contribute to recruitment challenges.

2.2.1.1 Investigator Factors

i. Poor Communication

Investigators may have difficulties in communicating the aims and concepts of a clinical trial to potential participants (11).

ii. Workload

The recruitment process for RCTs might overload investigators. It has been reported that there were difficulties following the study protocol (trial too complicated), completing the follow-up requirements, and obtaining informed consent from potential participants (14).

iii. Lack of awareness of appropriate clinical trials

Physicians may not always be aware of the clinical trials being conducted in their health institutes. Some clinicians may not be aware of the local resources available or may assume that none of the clinical trials would be appropriate for their patients (8).

iv. Unwillingness to "lose control" of a person's care

Most doctors feel that the relationship they have with their patients is very important. They want what is best for the patient, and if the patient participates in a trial, doctors fear they may lose control of his/her care (8).

v. A belief that standard therapy is best

Many health care providers may not adequately understand how clinical trials are conducted or their importance. Some believe that treatment in clinical trials is not as good as the standard treatment. Investigators might be uncomfortable admitting that there is uncertainty about which treatment is best in a phase [III] clinical trial (8).

2.2.1.2 Participants Factors

i. Misconception about the study

The well-known challenges are false to believe in health research and the lack of knowledge about the clinical trial process. This has led to mistrustful attitudes based on personal experiences with staff, nurses, and physicians at health institutions; and misinterpretations because of poor communications and low education status (18, 21).

Various potential participants fail to enroll in trials because of negative opinions and undesirable influences from the media (4, 17). Suspicions and fear of being treated like “guinea pigs” or “experimented upon” (8, 17, and 21).

Long-lasting anxiety and doubt exist among vulnerable populations like prisoners, race, children, women, elders, etc. about health research since exploitations happened in the past such as in the Tuskegee syphilis study (8).

ii. Lack of Awareness

A recent systematic review by Abraham and colleagues identified reasons for loss of interest of eligible participants to participate in a clinical trial; the main being inability to comprehend the concept of complex and demanding clinical trials (14).

A survey showed only 20% of cancer patients were aware that clinical trials could be an option for them which suggested the need for creating public awareness about clinical trial implications to improve participants’ recruitment (22).

A report showed that 40% of adults did not know the concept of the clinical trial process (22). A study done in the US showed that only 34% of 1,013 adults had heard about the clinical trials (40).

iii. Lack of Access

Usually, patients don't have information on the existing trials nearby that could potentially be helpful for their complaints. Investigators should make sure that the trials to be conducted in a given community are well communicated. The perception that there are no existing trials nearby discourages many potential participants. In addition, seeking care at a distant site results in time and travel challenges (8, 17). There are always limited resources, and participants may miss provisions from the trial coordinator (5).

iv. Personal Objections

Costs of being away from work and family may be deterrents for some people. Others may not wish to leave the care of their own physician. The trial may be more inconvenient for participants because of the inability to take time off to attend follow-up visits (14). Moreover, time constraints, distance from the study site, transportation issues, interference with work, or home responsibilities are also reasons for not be willing to participate in trials. People from certain racial or ethnic groups or who are medically underserved may feel that care within a trial will not be sensitive to their needs and fear exploitation by being vulnerable populations. A small number of studies have scrutinized the challenges of recruiting participants from different socioeconomic status (8, 21). People from various cultural or ethnic backgrounds hold different values and beliefs that may be different than the principles of Western medicine (8). Participants may be concerned about taking medication and experiencing adverse events (9). In addition to this patients may have a lack of interest in the study (11).

v. Insurance or cost problems

Fear of being denied insurance coverage for participation in a clinical trial could also be a problem. If a person is uninsured, the cost of trial participation is an issue (8).

vi. Language or literacy barriers

Language or literacy barriers may be difficult for some people to understand and consider participation. The complexity of forms, including informed consent documents, may also be a barrier to those considering participation. Translation can also be difficult if the person translating information has not had specialized training (8). The education of participants and his/her family members determine the understanding of clinical trials (4).

2.2.1.3 Protocol or trial-specific recruitment problems

Low recruitment difficulty may be associated with stringent eligibility criteria and inadequate budget allocation to trial sites. Therefore, stringent eligibility criteria and budget breakdown should be revised carefully to improve recruitment (14, 15). Excessive demands on participants like frequent appointments, long study participation, and inconvenient /uncomfortable procedures may also affect recruitment (9).

2.2.1.4 Organizational factors

A qualitative study conducted in the UK in 2015 to identify and examine staff views of the key organizational barriers and facilitators for patient recruitment identified four organizational factors: i) research competition, ii) rigidity between clinical and clinical research workloads, iii) perception if research team on an imbalance between patient personal burdensome and profit, and iv) poor techniques of recruitment skills and relationships among clinical research teams (19).

2.2.2 Recruitment Strategies

Effective recruitment requires an adequate study period to plan, create community awareness, and good communications (18). A comprehensive recruitment technique should be established and designed in detail to answer research questions (14). Strategies depend on the type and complexity of the trial, timetable goals, study settings, and others. (23).

Unable to meet the target sample size leads to a major challenge to the completion of clinical trials. Uncertainty happens concerning the relative success of various strategies to improve recruitment (13).

i) Registries

Many databases register a list of active clinical trials. These databases can be used to create awareness of physicians and patients on existing trials (18).

ii) Know the Target Audience

Knowing exactly whom the trial is targeting will help us to better refine our recruitment techniques (17).

> **For example**, if we plan to recruit the elderly, we should not advertise it on websites and social media since the study participants may not be familiar to use these media or have access to the internet. Similarly, if the study participants are children, we should not stick posters on hospital walls.

iii) Investigator strategies

A recruitment coordinator should develop strong professional relationships and good communication with the clinical manager and data coordinator to facilitate monitoring of the success of recruitment and particular strategies (18).

Investigators should be diligent and have work integrity, and good outstanding interpersonal skills would include the skill to be positive, to give compassionate respectful care (19).

Investigators' attendance in health conferences health programs on TV, radio interviews, and related forms would improve the recruitment process (18). Investigators should give participants written information sheets (14).

iv) Building the trust of participants

Respect for participants and their relatives can help build confidence and good relationship (1).

v) Be Timely and Responsive

A recent study showed that trial sites that waited for follow-up with patients experienced a 68% decrease in participation compared with those which followed up within a day of referral (17). The

longer a prospective participant has to wait before hearing back from study staff, the less likely it is that he or she will ultimately enroll in the study (23).

vi) Maintain Open Communication

Communicating with potential participants could help improve their capacity of understanding informed consent. Health care providers, clinical trial sponsors, the media, and the public must maintain open communication to overcome real and perceived barriers to clinical research participation (8).

The message should be precise but comprehensive to convince participants to participate in the trial (17).

vii) Media

Many pieces of the literature suggest media as the easiest way to approach clinical trial participants (12, 14, 17, 18, 20, and 24). Today's technology allows us to reach more people than ever before. Making sure to leverage all media outlets while planning recruitment initiatives and make recruitment easier and faster. Some great channels for reaching patients include Phone calls, chart reviews, TV, and radio, direct mailings, website, or social media, advertisement/articles in newspapers/journals; radio interviews, TV, advocacy groups, newspapers, internal databases, health fairs, posters at hospitals and clinics and hospital or Insurance newsletters.

viii) Organizational Strategies

Organizational strategies include making inclusive and full participants eligibility criteria for recruitment; avoiding stringent eligible criteria. Creating community awareness about clinical trials and encouraging community engagement. Before the commencement of the study, there has to be a recruitment plan that details the process of recruitments, required recruitment budgets to train recruitment staff, advertising the study, and other expenses (11, 13, and 23).

ix) Direct Mailing

Direct mailing is one way the improvement of recruitment (12, 14, 16, 18, 20, and 24).

Mass emailing has become an integral part of an overall recruitment plan in many clinical trials. To communicate wide populations, the mass mailing is quite cost-effective and can address large

numbers of participants with short notice. Individual letters, frequent phone calls, and well-organized media campaigns (e.g., print, radio, and video) have improved both the efficiency and the effectiveness of this strategy (18).

The recruitment letter should be clear and include information on the selection criteria and advantages and disadvantages of participation in the trial. Also, it should let the person know how to inform someone if he or she wants to participate, not to participate, or where to get answers to additional questions, and, of course, who is doing the study and why (24).

x) Incentives

Existing literature and studies recommended participants to compensate for their time and transport expenses to come to the study sites (12-14, 20, 25).

Though financial incentive facilitates participants' recruitment, it poses ethical issues like undue influences to participants' decisions making process. If the ethics committee approves the financial incentive, it should be provided at the study closeout to avoid early dropping out of the study (14).

xi) Referral

Cultivating potential sources of referrals to the study, networking with clinic a staff who is not working on the study, as well as with other local health care providers, and sending direct mailings to selected health care providers will improve recruitment (14, 23, and 24).

2.3 Retention

Retention is a continuing process and it is a way of guaranteeing that participants go through study procedures at the required follow-ups, complete questionnaires, participate in any other activities required by the study protocol and attend follow up appointments as needed (23). Retention involves establishing good relationships with participants to encourage them continuing participation (1).

A loss to follow up in randomized clinical trials may result in under-powering data to detect the significant difference between the groups (14).

Failure to retain an adequate number of participants in the trial may intimidate both the internal and external validity of clinical trials (15, 32, and 33). A high rate of loss to follow up may

introduce bias; outcomes may not be due to treatment effects but rather to a disproportionate loss of potential participants who were relatively symptomatic or asymptomatic to the study medication than other participants.

Moreover, high loss to follow up may result in actual differences between participants who stay in the study, and those who withdraw thus prevent the generalizability of findings to the wider population (23, 26).

2.3.1 Retention Challenges

After participants have joined the study, it may be difficult to keep them. Many unforeseen challenges can cause participants to drop out of the study compromising the sample size. When patients decide they no longer wish to continue with a trial, they could formally drop out and let the investigator know of their wishes, or they could just "disappear," never showing up for appointments again or returning any communication (17).

Earlier research has shown that high study demands such as frequent appointments, long study periods, and painful procedures, travel costs may discourage participants from staying in the research. Participants' fear of taking medication and experiencing side effects may also create dropout rates. Anxiety, low socioeconomic condition, and low education status, lack of social support, and a vulnerable population could also contribute to retention challenges (9).

2.3.2 Retention Strategies

Cramer et.al reported that "the success of clinical trials is contingent upon adequate retention of research participants" (42). Meeting recruitment goals without fulfilling retention requirements can be a major threat to internal validity. To retain clinical participant's several routines and non-routine strategies can be implemented (15).

2.3.2.1 Employing Routine Strategies

i) Create a Welcoming Environment

The primary step to improving retention is to make participants involved with the study as good and pleasant as possible. Friendly and polite staff is the least requirement for creating a welcoming environment. An easy-going and appreciating attitude is important for participants. Privacy is also important to keep the participants' information confidential. Other gestures such as offering coffee or tea can be made as well (9, 26).

Since patients are volunteering for the study, try to be as cooperative as possible. Is your waiting room inviting? Think of how your clinic is presented to the patient. Is it somewhere you would feel comfortable? (17).

ii) Establish an Efficient Tracking System

McCrady B et al. stated that "retention depends on being able to trace study participants" (43). Participants are asked to give telephone, home, and email addresses and mention the convenient times to contact them. Furthermore, detailed addresses of three people who can be communicated to trace participants are also required; a written informed consent would be obtained from these individuals. Confidentiality will be kept at all times (9).

iii) Educate Participants about Their Role as Research Participants

Potential participants are provided about different items of treatment and research demands during the procedures of consenting. However, there are different techniques to improve retention, it is essential to emphasize the implication of research follow up even though participants decide to withdraw from the treatment intervention. Expected challenges for missing visits are lack of transport, big festivals, work schedules, and family-related can be revised and resolved (9, 15).

iv) Establish Routine While Maintaining Flexibility

To improve medication adherence creating a routine for taking treatment and scheduling frequent visits can reduce missed visits due to forgetfulness. Reminder letters and phone calls have to be used for all appointments. Flexibility in scheduling follow-up dates that might be required to retain participants enrolled in both the treatment and evaluation of the study (2, 9, 26, and 28).

2.3.2.2 Employing Non-routine Strategies

Non-routine strategies are used when participants are not responding to the trial and routine strategies have not produced an encouraging outcome. This strategy is used when participants who repeatedly cancel visits without advance noticing, fail to come for planned appointments and show a wish to withdraw from the study.

- ***Staff Training***

Existing works of literature and researches recommend staff training to enhance the retention of clinical trial participants (9, 15). The clinical trial team must be trained on the study protocol and ready to identify and resolve adherence difficulties in clinical research by a) conducting an adherence assessment, b) formulating a working hypothesis for attending adherence issues, c) developing a range of options for addressing adherence issues, and d) implementing and evaluating risk reduction strategies. The content of training includes: familiarize participants with the follow-up, tracking an adherence history, determining research burdens, and addressing adherence issues (9).

a) Conduct an Adherence Assessment

An effort must be made to conduct face to face or telephone assessment interviews to trace the non-adherent participants. Participants who are not quick to respond to phone calls wishing a follow-up appointment must be sent a strategic letter and find out the participant's reason for not showing up. In the assessment interview, the clinical trial teams look for causes that deter participants from attending follow-up (9, 15).

b) Formulate a Working Hypothesis

As soon as participants have talked about their worries, the clinical trial team articulates a working hypothesis to address non-adherence. To have an agreement with participants, clinical trial teams should list all prospective risk factors that may affect adherence. Then participants are asked to mention and explain potential challenges to adherence. They are also asked to rate which challenges signify the highest difficulty to their adherence (9, 15).

For example, many participants are very concerned about data confidentiality which is to be the main cause of non-adherence.

c) Identify a Range of Options for Addressing Adherence

If obtaining agreement with participants succeeded, prospective solutions might be deliberated to solve no-adherence. One of the strategies is maintaining a balance between study high demands on participants. Most of the time participants are going through different hardships such as family, social, and economic problems and they find it very hard to meet the high demands of the study. During times of hardship minimizing the study's high demands can be very important in supporting participants and encourage their participation.

Barrett et al. reported that rescheduling follow-up appointments for participants who are going through hardships are the best approach to retain them. But for participants who want to withdraw from the study, the clinical trial team should assist them to delay their decisions and to let them know that they can give a thought and come back the other day. This gives a chance for participants to solve their problems and join the trial as soon as they can. However, it is a must to set a deadline for participants' final decision (9, 15).

- ***Use of Strategic Letters***

If participants are unable to have face to face or respond to phone calls, strategic letters used as an important means of communicating with participants (9, 15, 26). The strategic letter should comprise the rationale for participants being in the study and declare the importance of the research interview to complete the study.

- ***Role of coordinating center in facilitating retention***

The clinical trial site is responsible for training retention strategies. The site should also improve clinical trial team enthusiasm and compassion attachment with participants, strategies in meeting high retention rates (23). After training, on-site visits monitoring should be planned. During monitoring reliability and credibility, the confidentiality of participants' data must be assessed to measure the study's progress. Study sites not achieving the goals are provided with comments to improve the retention rate. Comments might include promoting tracing techniques and the study site to be a welcoming environment, the clinical trial team should develop a rapport with participants (9)

2.4 Conceptual Framework

Figure 1 shows a conceptual framework that represents the synthesis of study literature on how the variables were interrelated. It maps out the challenges and strategies for recruitment and retention of participants in clinical trials.

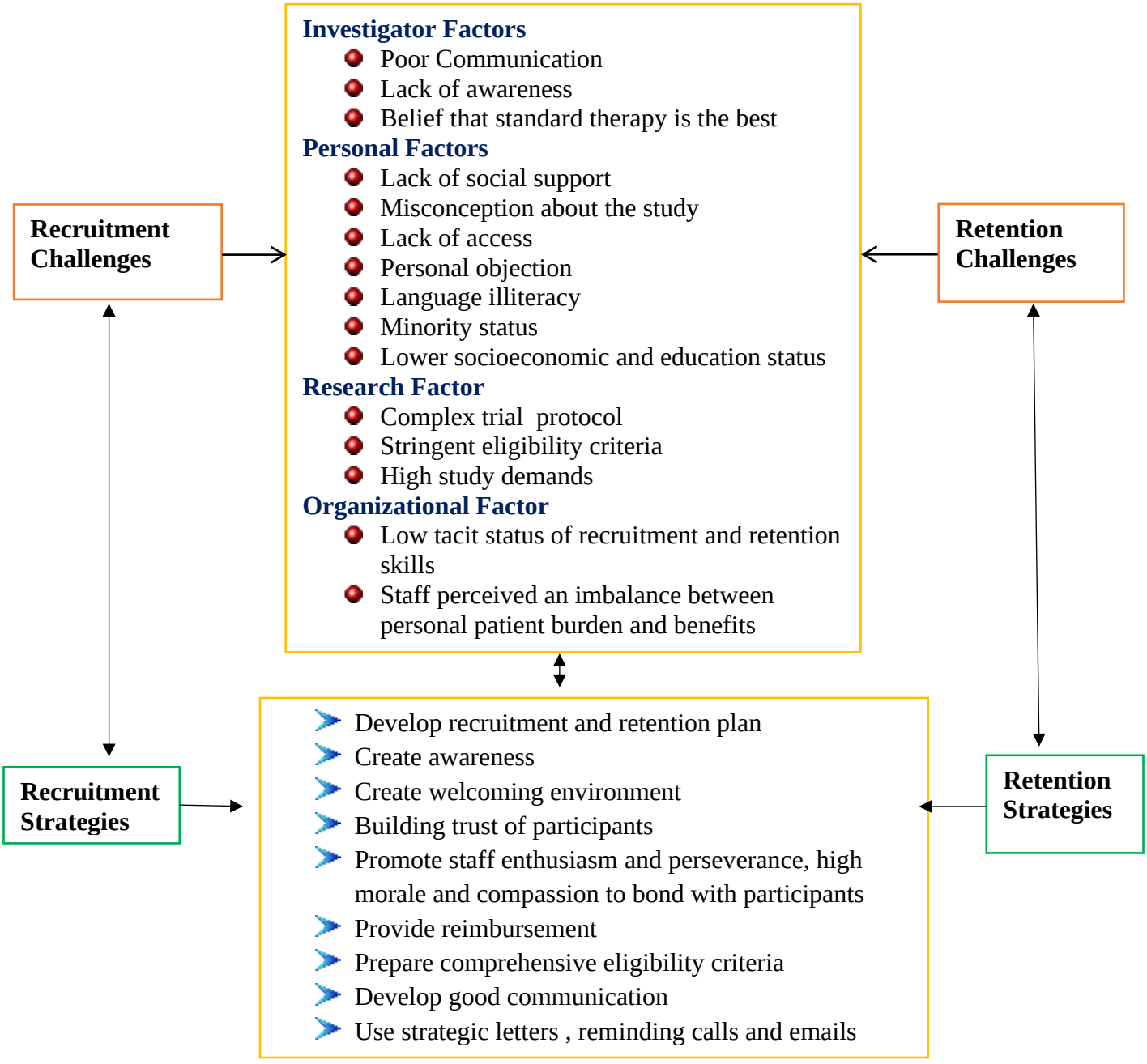

Figure 1*: Conceptual framework of challenges and strategies for recruitment and retention of participants in clinical trials*

3. Objectives

3.1 General Objective

The objective of this study was to identify and synthesize all potential challenges and strategies for enhancing the recruitments and retention of participants in clinical trials in Ethiopia.

3.2 Specific Objectives

1. To assess detailed potential challenges and strategies for recruitment and retention of participants in clinical trials in Ethiopia.
2. To provide guidance that improves the recruitment and retention of participants in clinical trials in Ethiopia.

4. Research Methods

4.1 Study Settings and Period

The study was conducted in the following five clinical trial sites selected for their work in clinical trials:

Armauer Hansen Research Institute (AHRI) – The establishment of a clinical trials unit in 2001 is one of the major milestones in the history of **AHRI**. Currently, the clinical trial has its own clinical trial team, its screening and admissions wards, and laboratory.

Zewditu Memorial Hospital – The hospital had conducted a WHIP3/Tuberculosis(TB) challenge Tuberculosis study. WHIP3/TB is a collaborative clinical trial project with Aurum institute funded by the U.S. Agency for International Development and led by Ohio State University with support from the Global One Health initiative and Office of Sponsored Programs.

Addis Ababa University– The College of Health Sciences has led several clinical trials and hosts one of two institutional review boards recognized by the World Health Organization (WHO) / Special Programme for Research and Training in Tropical Diseases (TDR) Strategic Initiative for Developing Capacity in Ethical Review. Center for Innovative Drug Development and Therapeutic Trials for Africa runs clinical trials training programs and runs several research projects.

Jimma University Teaching Hospital – It has been working in malaria clinical trial in collaboration with the Medicines for Malaria Venture since 2014. Jimma University has inaugurated a new clinical research center at Agaro General Hospital.

University of Gondar Hospital – Has been involved in clinical trials for leishmaniasis and malaria for many years. The Dabat Research Center is the first three Research Centers at the University of Gondar; established in 1996, to create a platform for research and academic excellence in public health and produce evidence for policy implications. The second Research Center is Leishmaniasis Research and Treatment Center; established in 2004.

4.2 Study Design

A qualitative study design was used for this study. This study design is suitable to find out the meaning that people give to events that they practice (34). A qualitative design would thus be important to explore challenges and strategies related to recruitment and retention of participants

in clinical trials. The views of principal investigators, trial physicians, trial nurses, and trial coordinators were explored in a face to face interviews. The views of trial participants were explored through telephone interviews. The study was conducted from February 28, 2020, to April 29, 2020.

4.3 Study Respondents

A total of 19 respondents were included. Five principal investigators, two physicians, two nurses, seven coordinators, and three trial participants were selected. The interview ranges from 11 to 50 minutes and the average interview time was 25.4 minutes.

4.4 Eligibility Criteria

- Clinical trial investigators, trial physicians, nurses, and coordinators who were involved in participants' recruitment and retention processes in Ethiopia.
- Clinical trial investigators, trial physicians, nurses, and coordinators who were involved in follow up arrangements and counseling participants in Ethiopia.
- Participants/patients who were or being involved in clinical trials.
- Individuals who were volunteers and gave informed consent.

4.5 Sample size

Interviewees were purposively selected from the five study sites. The sample size was determined based on the principle of theoretical saturation; when the information collected beings redundant. The interview continued until theoretical saturation was achieved when 19 respondents were recruited and additional interviews were thought redundant (41). Initially, ethical clearance and supporting letters were submitted to the designated five institutions. Study respondents were selected using purposive sampling with the support of their respective institutions. A total of 22 potential candidates were invited. Among them, 19 were involved We communicated with 16 respondents through email as well as visited their office and schedule an appointment for an interview. The other 3 respondents were approached with the help of trial physicians and nurses. They had given detailed information about the purpose of the study and confidentiality. Then we interviewed by telephone. The rest of the 3 potential respondents replied that they couldn't make it for certain reasons.

4.6 Data Collection

Data were collected through face to face (16) interviews among trialists and through telephone interviews (3) among trial participants. Interviews were conducted in Amharic and English. All principal investigators (n=5) and one physician were interviewed in English. The study principal investigator conducts the entire interview. The rest of the respondents (n=14) were interviewed in Amharic. Interviews were audio-recorded. However, trial participants weren't willing to be recorded. Interviews were guided through a semi-structured topic guide that was developed on an initial literature review attached in Appendix IV: Questions and Closing key Components~~Appendix IV: Questions and Closing key Components~~. The guide included questions about the challenges and strategies of recruitment as well as challenges and strategies of retention. The interview guideline was pretested with two individuals. Names of interviewees were not used at any phase of the data collection process to ensure confidentiality. Each interviewee was allocated a unique identifying number written on the interview form, in notes taken, and was used to name audio files and transcript documents. The format for naming files is attached in Table 1 Respondents Sociodemographic~~Table 1 Respondents Sociodemographic~~. An audio recording was carried out after obtaining the consent of the interviewee. The interviewer recorded a summary of each interview at the end of each day or the next day.

The principal investigator did the translation and transcriptions were done with five individuals. Amharic audio recordings were listened to carefully and then transcribed and then translated to English as well as English audio recordings were listened carefully and then transcribed. The translator had attempted to express the meaning of the source language (Amharic) within the natural grammar of the target language – English. Each transcript was checked by the principal investigator by listening to sections of the recordings and cross-checking the transcription, or reading sections of translations and verifying these with the original language texts.

4.7 Data Analysis

Data organization and analysis were carried out using qualitative data analysis software, Open Code version 4.02.

Upon completion of each interview, data files were imported into the new Open Code. Transcripts were coded by reading data line-by-line, and then later developed themes and theoretical constructs

by grouping the base coding together. Caution was taken to make sure that codes precisely apprehended the participant's views.

Following the coding process, a thematic analysis was conducted to identify, analyzing, and reporting the data sets. Themes and theoretical constructs were developed from both the field notes and the interview transcripts. A coding book was developed from a few of the initial transcripts and was used to code later transcripts in an on-going process as data were collected. As more transcripts were coded, the codebook was further refined to reveal any new emerging ideas or themes. The on-going analysis was characterized by frequently going back to transcripts to ensure the text was coded within the context.

4.8 Ethical Consideration

Before the commencement of the data collection process, ethical clearance was obtained from CDT Africa Scientific and Ethics Committee, College of Health Sciences, Addis Ababa University (reference number CDT/165/20).

Written Informed consent was obtained from all respondents after providing relevant information about the study, including the objectives of the study. Consent was obtained from trial participants with the help of their physician's and the interviewer contacted them through telephone during their follow-up dates. Confidentiality and anonymity were maintained.

4.9 Data Presentation and Dissemination

The result of this study will be prepared both in soft and hard copy as well as disseminated to CDT-Africa, Addis Ababa University/College of Health Sciences and it will also be submitted for publication and present to all concerned stakeholders.

5. Results

5.1 Socio-demographic characteristics of Respondents

Most respondents had a college education and involved as principal investigators, and trial coordinators, physicians, and nurses. Fifty-three percent (53%) of the respondents hold a master's degree. Only one respondent hasn't attended formal education. Most of the respondents were public health specialists (26%) and most of them were involved in the clinical trial as trial coordinators (37%). The numbers of females were slightly greater than that of males. The socio-demographic characteristics of respondents are given in Table 1~~Table 1~~.

Table 1 Respondents Sociodemographic

Characteristics	Frequency	Percent
Sex		
Male	9	47
Female	10	53
Education		
PhD	5	26
MSc	10	53
MD/BSc	2	11
Elementary school completed	1	5
No formal education	1	5
Profession		
Physician	4	21
Pharmacist	2	11
Public health specialist	5	26
Nurse	2	11
Microbiologist	1	5
Biomedical	1	5
Medical science laboratories	1	5
Teacher	1	5
Carpenter	1	5
Housewife	1	5
Involvement in clinical trials		
As a principal investigator (PI)	5	26
As a trial coordinator (TC)	7	37
As a trial physician (P)	2	10.5
As a trial nurse (N)	2	10.5
As a trial participant (TP)	3	16

5.2 Challenges and Strategies for Recruitment and Retention of Clinical Trial Participants

The findings are categorized into two: Challenges for Recruitment and Retention trial participants as well as Strategies for Recruitment and Retention of trial participants.

Emerging themes from the thematic analysis resulted in the generation of three main themes and ten sub-themes.

Table 2 Study Finding Categories and Themes

<table>
<tr><th colspan="2">Findings Categories</th><th>Challenges for Recruitment and Retention of Trial Participants</th><th>Strategies for Recruitment and Retention of Trial Participants</th></tr>
<tr><th>No.</th><th>Themes</th><th colspan="2">Sub-themes</th></tr>
<tr><td>A.</td><td>Clinical trial team factors</td><td>Subthemes
Communication Related
✶ Poor communication
✶ Lack of knowledge about research among health professionals
✶ Mistreating participants
System Related
✶ Poor referral system</td><td rowspan="3">Subthemes for the three main themes
Promote clinical trials
✶ Create awareness
✶ Provide training to the clinical trial team
✶ Use Media
✶ Encourage community engagement
✶ Establish community advisory board
Improve Communication skills
✶ Clarify the purpose of the study
✶ Develop compassionate respectful care
✶ Have a positive approach
✶ Establish an efficient tracking system

Improve clinical setting system
✶ Choose an appropriate site
✶ Improve referral system
✶ Use flexible management of participants
A good estimation of cost
✶ Reimbursement</td></tr>
<tr><td>B.</td><td>Participants factors</td><td>Subthemes
Communication Related
✶ Misconception about the study
✶ Low education level
✶ Lack of awareness and knowledge about the study
Interest Related
✶ Lack of research Interest
✶ Lack of social support
✶ Participant moves around</td></tr>
<tr><td>C.</td><td>Study Factors</td><td>Subthemes
The complexity of the study
✶ Long questionnaire and assessment
✶ Stringent eligibility criteria
✶ Extra, and inconvenient procedure
✶ Frequent appointment
Cost related
✶ Require big investment</td></tr>
</table>

5.2.1 Challenges for Recruitment and Retention of Clinical trial participants

A. Clinical trial team factors

This theme emphasized on respective challenges of recruitment and retention related to clinical trial teams which were mentioned by the respondents during interviews.

Communication Related

Under this subtheme, most study respondents stated that communication skills associated problems among clinical trial teams were one of the factors for low recruitment and retention.

Poor Communication

In the following quote, a trial participant spoke about how poor communication would have affected her decision making if she had not met another trial participant in the cafeteria. Also, principal investigators explained how poor communication affected the accrual rate.

> *'…. the first Dr. who communicated with me, he had explained the treatment options in the clinical trial; unfortunately, I did not understand and did not believe him. However, the woman I met in the cafeteria that was already in a clinical trial as a participant had explained in detail and clarity about the study. The woman I talked to hmmm… she was sent from God, I believed that if it wasn't for her I wouldn't be here today…' (TP 017)*

In the following quote, a principal investigator explained what caused the poor communication among study staffs with participants in the following quote:

> *'….the data collectors could not explain the trial. So, participants were just given a small amount of information and invited to come…' (PI 004)*

Mistreating participants

One principal investigator and two trial coordinators emphasized the effect of mistreating participants in the study.

> *'...we need to consider that participants talk to each other so if you treat one participant wrongly you may lose the entire participants; so treating every single participant*

respectfully and discussing with them about the study in detail in the consent process for me is the key to everything…' (PI 001)

…the interaction we had with the study participants has a great effect. If we had mistreated participants, they wouldn't have come to follow up and not prefer to see you again… (TC 010)

…if you mistreat them they will have a very low probability to come back hence we need to approach them with politeness and respect… (TC 012)

Lack of knowledge about research among health professionals

Lack of knowledge about clinical trial research among healthcare professionals was one important barrier to recruitment.

…even the health care professionals have no detailed knowledge about research and they consider that clinical trial is all about only making experiments. So during recruitment, they had difficulties explaining what clinical trial is to their patients… (PI 002)

…our attitude about the research towards research is not much; we don't have much knowledge to explain clinical trials to potential participants… (TC 013)

System Related

This sub-theme presented system related difficulties. Most of the study respondents explained how poor system affect their recruitment goals.

Poor referral system

It is poor networking with clinic staff who is not working on the study, as well as with other local health care providers thus health centers don't have awareness about existing trials as result there will be a poor referral of a potential patient to the trial site. Responses from a trial coordinator showed that on how poor referral systems affected the recruitment goals.

…we had few challenges related to the poor referral system. We had a plan to recruit 100 patients with MDR-TB within two years and we used a referral system to recruit potential participants. Therefore, we met stage I recruitment goal with 50 participants but we

couldn't even achieve half of it for stage II; and it was because of a poor referral system… (TC 011)

…the other is poor referral system is one of the challenges. The recruitment staff failed to send potential participants as a result of poor communication of the existing trials… (TC 006)

B. Participants factors

This theme presented particular challenges of recruitment and retention related to participants such as misconception of a clinical trial, low education level, lack of research interest, participants' moves around, lack of knowledge, and awareness about clinical trial accounted for low recruitments and retention.

Communication Related

Most of the study respondents listed many communication-related difficulties among trial participants. This factor was considered to be the main challenge to succeed trial recruitments and retention plan till the study closeout.

Misconception about the study

A misconception about the study was considered to be a major challenge for low recruitment.

…some trial participants thought that we would exploit and do experiments on them. Sometimes their family spread false rumors about the clinical trial and hampered their siblings' decisions… (TC 010)

...many participants have biased information about the trial, they were trying to relate with bad spirit. They thought that we are going to use their blood samples for another use besides what we have been telling them… (TC 007)

Also one of the principal investigators said that a clinical trial was intervention research and participants perceived as they would be used for the experiment.

…in general, many people have misconceptions about research. When you come to clinical trials, it is another level of challenge because it is an intervention study and people perceive it as a kind of using participants as lab animals just for experimentation… (PI 015)

Low education level

Research team members repeatedly said that communicating the concept of a clinical trial to study participants who were not educated was a setback.

> *…participants don't know the research and clinical trial, especially when it is about the drug trials, that's another problem. It is very hard to describe clinical terminology for them. For example, we found it hard to explain the concept of randomization to them… (TC 012)*

> *…people who live in a rural area are the illiterate one or don't understand the concept… (TC 007)*

Trial coordinators also stated that researching a rural area was very challenging and it made worse the situation.

> *…when you do clinical trials especially in a rural area, one of the challenges is many illiterate communities can't read and write… (TC 013)*

Moreover, one principal investigator underlined the clinical settings in which the study had been conducted were found in communities with a low level of education.

> *…in our setting, communities are not educated well and the knowledge about clinical studies is very poor… (PI 016)*

> *…I think that people still say yes to being in projects and I suspect over time people will say no because it is difficult for them to understand what that means. And I think it is not right that we're asking people where they may not fully understand everything… (PI 004)*

Lack of awareness and knowledge about research

Many respondents observed a lack of awareness and knowledge among trial participants. They considered lack of knowledge to be one of the main challenges during recruitment and retention.

> *…just how difficult it is to get to inform people in a way that is meaningful and understandable for them and you know their background and previous experience doesn't make it easy for them to sort of make sense of what this is…so it is truly challenging… (PI 004)*

…patient may not make a distinction between treatments and being part of a trial. So the level of awareness about clinical trials why they need to go into research or trial is poor. Then it is too complicated for them to understand … (PI 016)

Trial coordinators and trial physicians talked about a lack of awareness of communities about the research concept.

…one of the challenges was the lack of awareness about clinical trials and general concepts… (TC 011)

….there is a lack of awareness about clinical trials in the community… (P 014)

Interest Related

In this sub-theme, study respondents were mentioned that the community showed no interest to be involved in the research work.

Lack of research Interest

A trial nurse and trial coordinators indicated that people who seek medical care in hospitals for their illness didn't show interest to be part of the proposed research. They only got clinical services.

...first of all people don't have interest in the research… when you tried to give them clear messages and if they found out that it is about research; they wouldn't sit and listen to you. They don't even give you time. They spoke that they visited a hospital for their regular check-up not to take part in the research.… (TN 009)

Also, trial coordinators said that the community lacked interest in research so that they did not encourage family members who had the interest to participate.

…. another challenge was the community's lack of research interest. Even though she/he showed interest to participate; their families may not be enthusiastic about the study… (TC 011)

Lack of social support

Many respondents articulated a lack of social support as a key factor for low recruitment and retention. Trial participants lacked support from their spouses, families, and neighborhood. The trial coordinator quoted the following;

> *… another challenge was participants' family; some participants hide about themselves being in the study. Their family will tell them that's not a good decision and discourage from… (TC 011)*

The principal investigator stated that they had a hard time making reminder calls to participants.

> *…we don't want to ring the woman experiencing intimate partner violence may be the mobile phone is owned by her husband. And so we don't want to call her so that we have to be careful… (PI 004)*

A trial physician stated that there are participants who wanted to have a discussion with their family about the study. After they took the information sheet, they would be lost.

> *…people want to discuss the information sheets with their family especially women who want to talk to their husband and later they wouldn't show up to the trial. When we tried to reach out to them through the telephone; they told us that their husband wasn't willing… (P 014)*

Participants travel

The principal investigator and trial coordinators stated that participants moved around to visit their family and friends for holidays and different festivals.

> *…trial participants travel. They are active economically and you know they visit friends, they have weddings; they have what not… (PI 016)*

C. Study factors

In this theme, all respondents pointed out the different research/study factors, which negatively affected recruitment and retention processes.

The complexity of the study

Under this sub-themes, all respondents have spoken about the complexity of the study-related factors such as long questionnaires and assessment, stringent eligibility criteria, extra and inconvenient procedures, long waiting time, and frequent appointments.

Long questionnaires and assessment procedures

Trial coordinators and participants said that long questionnaire and assessment procedures were one of the challenges they encountered in the trial. Trial coordinators quoted below that the trial safety and efficacy assessment is too long.

> *…there are a lot of things that you need to measure/ assess and these things sometimes bother them; it might not be something that they are used on the regular treatments follow-ups so I think these are the things: long questionnaires and procedures you need to perform the safety procedures and also the efficacy assessments: the safety and efficacy assessment they usually are large a lot of assessments are done so it sometimes bothers them… (TC 003)*

One trial participant emphasized that he stayed long in hospital after that he had difficulties going back home.

> *…we went through long questionnaires and assessments. That was very difficult to stay for a long hour in the hospital. There is transport shortage to go back home; usually, I arrived home late at night... (TP 018)*

Stringent eligibility criteria

There was concern that a stringent eligibility criterion does exclude potential participants.

> *….our previous trial project had very stringent recruitment criteria and it was very difficult for us to recruit potential participants since most of the trial participants failed to meet the eligibility criteria… (TC 003)*
>
> *…for example one of the inclusion criteria was to include patients who had high and medium gene expert results, and we couldn't find more participants with high or medium index gene expert; as a result, we couldn't meet the deadline and achieve recruitment goals… (P 005)*

Extra and inconvenient procedures

Extra and inconvenient procedures were major challenges to retain participates until the study closeout.

> *…they don't want to have an intensive type of procedure like X-ray and giving blood samples… (TN 009)*

Also, physicians explained that participants did not want to have frequent blood sample procedures.

> *…for our study, there were times that we ought to take 5-6ml blood samples. Of course, some participants didn't like frequent blood sampling but we tried to explain to them clearly. Usually, they want to know the investigation results, so we interpret and tell their results. So, the other day they will be willing to give blood samples... (PI 014)*

In addition, one of the trial participants shared her first day experience during the recruitment process was very tedious.

> *… I was interviewed about my family and living conditions. I remember, in one day I had to go through many processes and questions. That was very boring…* (TP 017)

Long waiting times are also mentioned as one of the challenges for retention. Trial participants did not want to stay for long hours in hospitals for several reasons. A trial investigator talked about those participants who hated to stay long in the queue for a trial unlike for their routine care.

…most of the time it is in the queue that they wait long and they hate to wait in the queue for a study. In the care they can be in the queue; in a trial, you need to avoid that… (PI 001)

Furthermore, a trial nurse said that potential participant perceived being involved in a trial is an extra burdensome.

…I was working at central triage and many people were complaining that they had long waiting times during their regular follow up and coming to the trial station is another burden for them. And that was very challenging for us… (TN 008)

Frequent appointment

Principal investigators explained how frequent appointment affected their retention rate. However, it all depended on the relationships they had with the participants.

… the longer you follow the more difficult it is so there we had good follow to to18 months, so it depends on how close the connection is perhaps with the people you're following… (PI 004)

Also, a principal investigator stated that to make the follow-up convenient for participants first one should consider the project objectives.

...you have to weigh what the proposal wants and what the patient will be discomforted with. If science wants they should be followed every month; we have to do it, science has to be fulfilled. At the same time, you have to minimize so that participants will be satisfied. So, you have to weigh that one… (PI 001)

Cost related

Require big investment

Clinical research teams stressed that recruitment and retention needed plenty of money to invest.

…retention is pretty much resource intensive, you need to invest in it, you need to have the budget for and it is resources, budget, and time intensive… (PI 001)

This idea was also found in some of the replies given by principal investigators. They stated that there were many expenses to the closeout.

…there must be some resources to support recruitment and retention process so that; there must be a special provision to support such as logistics, human resources, and also the compensations to consider just not transport but also lost opportunity and that has to be calculated and if that can be available it would help… (PI 016)

5.2.2 Strategies for Improving Recruitment and Retention of Trial Participants

Choosing appropriate sites, creating awareness, developing rapport, using referral systems, clarifying the purpose of the study, reimbursement, and establishing an efficient tracking system were major recommendations by respondents to improve recruitment and retention.

i. Promote clinical trials

Below this sub-theme, all respondents gave weight to promoting clinical trials. It was one of the important strategies to ease the recruitment and retention process.

Create awareness

They also stated that government and private institutions must be supportive in creating awareness of the community.

…Ethiopia Food Drug Administration, Science and Technology Minister, Minister of Health, and universities should play a big role in communicating and raising awareness about clinical trials… (TC 011)

Principal investigators said participants should be aware of the proposed clinical trials before they become part of the study.

…participants need to be aware of all benefits of being part of the study. So giving that general education for the community and health professionals both in service and out services… (PI 001)

The trial coordinator indicated that awareness should be created at all levels of any organization.

…awareness should be created about every single thing of clinical trials in the community, woreda, and hospital levels… (TC 011)

Furthermore, a trial coordinator suggested a technique to raise awareness: integration of clinical trial course in the education system.

…it has to be incorporated in the educational system or training but awareness creation is important… (TC 003)

Providing training

Most of the respondents mentioned this as a key strategy used to improve recruitment and retention. They suggested that all clinical trial team and referral site staff, especially those involved in the recruitment and retention process, should have training in GCP, participants handling and management, and bioethics and that the training must be given before the recruitment process for all staff members.

…staff members working in the recruitment receiving training before the recruitment process is the key. As I told you it is not only the staff member but beyond the staff member, facility; the hospital staff member also not only in recruitment….we can't move without having that… (PI 001)

Besides, trained health workers were able to deliver quality care for participants.

…health workers working in the clinical trial were trained and qualified to provide quality care for participants so the participants really enjoyed the follow-up and even after the completion of follow up they wanted to be engaged in research and asked, again and again, to continue… (PI 015)

Trial coordinators also explained that they had different kinds of training throughout the project.

…we were given training about GCP and GCLP. We also had training on study objectives. After this, we trained practically how to do it. Over time we were given repeated training whenever there is a protocol amendment… (TC 011)

…it is not one-time training for our staff member but we have to repeat that … (PI 001)

Also, the physicians gave details on the type of training they took.

…prior to any works in the trial, we took discipline and ethics, protocol, and SOP's training. I was hired in May and took these pieces of training for one month and in June I started screening and recruitment. I even did participants' role models on how to give consent and information and we tried to explore expected difficulties and challenges… (P 014)

Encourage community engagement

Principal investigators and trial coordinators emphasized the need for community engagement. If community engagement is enhanced recruitments and retention challenges will be solved.

> *…for recruiting participants, one has to take into consideration the involvement of the community. Community engagement is the most important in all trials, in all researches not only in clinical trials. And currently, we are doing that as an institution and also institution is developing a community engagement in the research. Once you develop that you can easily disseminate the information and you can easily inform the community that the research that you are doing is not to collect money or to harm anybody but for the benefit of the community. Once you have involved community recruitment will be easy… (PI 002)*

Besides, principal investigators recommended that engaging all stakeholders before the commencement of the study is a must.

> *…so community engagement is really important in this case. So we have to engage all important stakeholders during the study initiation and before the initiation. Stakeholders should be aware of the benefit, and implications of a clinical trial. Then, if all stakeholders understand the benefit of the study they can assist us. So engaging key stakeholders and engaging a community is important… (PI 015)*

Establishing a community advisory board

Well, experienced principal investigators and physicians stressed that the community advisory board would be used as a bridge with the community.

> *...what I can give you as a recommendation; it is not only in our country but what I have experienced in South Africa; they use this retention mechanisms community advisory board (CAB). These people were the ones who are working between the study participants and health professionals. For example, if someone in the community sick and has difficulties, this CAB will inform the health professional because he/she may talk bad things about the trial. Afterward, he/she might tell CAB. If he/she is lost from the study these CAB's will trace and find them. I recommended that this CAB should be implemented in our country. I hope it is good to have someone who can link the health professionals and the community.*

We have seen more than ten clinical trials and witnessed this CAB knew every participant's name and asked them if they are feeling any problems. They already build trust with the community. So when there is an unethical practice they will disclose and demand rights for the victim. They always make sure participants' rights are protected well… (P 014)

ii. Improve communication skills

Clarifying the purpose of the study

Participants suggested that giving detailed and clear information about the study would reassure potential participants. In addition, telling participants about their significant contributions to the community and world would make them feel valued.

…we make sure that they understand the purpose of the research. We also emphasized their future contribution to the world and country… (P 005)

…we explained the effect of clinical trials at individual and country levels. This helps to improve the existing drugs will benefit patient so when you keep telling this in detail; they will be encouraged… (TC 007)

…we tried to emphasize the importance of being on research more advantages for future generations… (TN 009)

In addition, most of the respondents also recommended this strategy as a very useful one for retention. They stated that participants should have clear and detailed information about the study. Communication must be made with the language that participants comprehend. If participants enrolled without understanding the study; they wouldn't stay long in the study.

…first of all your information sheets should be clear and understandable. You prepare the patient participant information sheet in understandable language. You have to translate to the local language, which the participant can understand. These information sheets should contain all the procedures that you will conduct and the period of the trial, and you will inform the participants of all that is needed in the protocol and also tell them the rights. So, if the participant gets this all information in the beginning it will be easy for you to retain them… (PI 002)

Media

Most of the respondents said that using advertisement was one way to promote existing clinical trials to the health workers and community. However, they claimed that promoting on social media and television might not be feasible in the Ethiopian context.

Principal investigators indicated that promoting the study was a useful strategy to encourage participants to visit trial sites.

> *...sensitize and advertise a clinical trial is one of the useful strategies to improve recruitment… (PI 001)*

Also, trial coordinator and physician said that using poster and brochures were useful to remind health workers to refer potential participants.

> *...we stick posters or give them a brochure about the study for clinicians to remind them along with their regular job that they do your recruitment or referral… (TC 003)*
>
> *...we display eligibility criteria posters in the hospital ward which are available for the hospital staff and patients… (P 014)*

However, participants argued that the media may not be a suitable technique in Ethiopia. They mentioned probable factors such as participants with low levels of education, cultural barriers, and messages may be misinterpreted. Although they explained that social media would have been an easy way to spread information within a short time and at less cost.

> *...I don't think it was very easy to get uptake. I think first of all not everybody is literate. I mean that's kind of a clear barrier, but I think there's more of a cultural barrier that people don't expect to kind of proactively read something in a clinic and there's not a traditional culture of doing that. So we weren't very successful with using media as a recruitment strategy, but I think it might depend on your client group, you know, given the lack of services in Addis and it wasn't very successful which was perhaps a bit surprising but where there are not many resources might it be… (PI 004)*

The level of awareness among the community was not satisfactory. Cautions must be taken to advertise any clinical trials through social media. It may be misinterpreted and would cause big damage.

… So using media and other kinds of outlets needs high precautions otherwise it may mislead the whole thing or it may raise the expectation of people; unnecessarily high expectations which will be a problem again so using this kind of strategy should be with very high caution… (PI 015)

Furthermore, the principal investigator articulated that the rural and deprived communities had poor reading habits and accessibility of written Medias.

…it is partly because we deal with as problems of rural communities; poor communities are you know the culture of reading and you know the distribution of you know written media is limited and as a result of that we didn't pay much attention about it newspapers, brochures and others…(PI 016)

Develop compassionate respectful care and rapport

All respondents identified this as a key strategy to recruit as well as retain participants. They explained that having a good relationship with study participants have a great effect on recruitment and retention.

A trial coordinator highlighted his experience on how to give compassionate respectful care to participants.

…the right way of approaching them had been great; we had developed a strong rapport with them. We put our feet in their shoe to understand their problem. We build a family like approach and we had to greet them wherever we meet them. Just in case if we hadn't greeted them, they would have considered that they were not respected and only useful for trial. So our relationships with them have been healthy. It is always recommended to greet and stay close with participants. Help them to pass through difficult times without additional burdens. Ask them about their daily challenges and follow them closely. The other thing is we are making sure that they have detailed information about the study during consenting processes… (TC 011)

Positive approach

Most of the respondents suggested that positive approaches would help all health workers develop a good relationship with study participants. This could build the trust of participants and improve good communications.

One of the principal investigators explained that the first approach you have with participants would decide whether participants would be willing to participate.

> *…approaching people in the right way is important. Especially if they understand what's happening, they feel valued and worthy for them to be involved, then you knew they would be committed to being in the study in the first place… (PI 004)*

Trial coordinators suggested that a positive approach was the main technique to get participants recruited.

> *…there were times participants being part of the study because they were very overwhelmed in the first approach with the health professionals. For example, there were health professionals he/she explained the consent to the study participants and they were not able to enroll a single participant because he/she fails to communicate very well. At the same time, there were health professionals who explained consent even to problematic participants and were able to enroll them… (TC 010)*

Also, trial participants shared the relationship they had with the clinical trial team

> *…we want to be treated in the right way and a positive approach is very important… (TP 017)*

Establish an efficient tracking system

Most of the respondents suggested that this is the strategy they used when the participants got lost to follow up. They made reminder calls and home visits.

> *…also make a home visit when they are enrolled in the trial our staff go and evaluate the home. They are in and for some reasons, if the patient is lost we also do home visit… (PI 002)*

Also, a principal investigator quoted that when participants didn't show up for an appointment, trial staff should make sure that the participants were fine; so they would visit them at home.

> *…for the big trial when people dropped out of care if they missed their appointment by more than one month to pick up their medication or the lay project worker did a home visit just to say oh did you remember? But also we should check for severe adverse events… (PI 004)*

iii. Improve the clinical setting system

Choose appropriate sites

Most of the respondents indicated that choosing a suitable study site was useful to have an adequate number of participants for the study. Principal investigators explained that disease prevalence is very important to consider the place for conducting clinical trials.

> *…the endemicity is important, the magnitude of the problem is important so if there are, for example, areas where we have the problem but not big enough and you know it doesn't help really to do it and partly because when a community engaged in a clinical trial we want the community to be aware of it; not just a few individuals. We want the public really to be part of it. We can do that only when we have sufficient numbers of patients, a community knows the health problems. When it is low magnitude/ sporadic diseases the people may not be even aware of that what the condition is and you know it is not actually to do it in those places… (PI 016)*

In addition, one of the principal investigators suggested that before choosing a clinical site a survey or feasibility trial should be done.

> *…strategy we used first we identified the high load clinical setup. We initially did a survey and study on the number of participants who would attend our study… (PI 001)*

Improve Referral System

A referral was one of the recruitment strategies mentioned by most participants. Trial participants talked about how they were referred to the study site.

…the pharmacists asked me if I was interested to join the awareness program which was organized by the new treatment center… (TP 018)

…after I came here, one of the doctors consulted me if I am willing to participate in the study… (TP 017)

Also, the principal investigator and trial coordinators indicated that hospitals were their source of participants. They used hospital health workers to screen the patients based on the eligibility criteria they were given.

…the primary strategies we used hospital health workers such as nurses, and other staff. So, when they find patients who fulfilled the eligibility criteria, they sent them to the study site... (P 014)

…we used hospital staff those who can easily access patients and give highlight about the research. If they are interested and willing, they would send us… (TC 012)

Flexible management of participants

Most respondents articulated that flexible management of participants, such as aligning their appointment with their regular hospital follow up and accept unscheduled visits was necessary.

...we used to align participant follow-up dates with their hospital regular visit day. For example, if you're enrolling HIV positive individuals, they have a regular schedule to collect their drug from the clinic. So aligning their trial follow up that with their routine hospital care is very good… (PI 001)

…even when the patient comes in unscheduled follow up just you have to treat and evaluate them, and this will help the participants to retain in the trial… (PI 002)

In addition, working on the weekend helped civil servant participants not to miss follow up dates.

…so you need to come up with a strategy like those who are working and not working; and at what time do they come sometimes from Monday to Friday. Patients are busy working on the workday and we have to ask our staff to work on the weekends so we have to be as flexible as we should to retain the participants…. (PI 001)

iv. A good estimation of cost

Reimbursement

Most of the respondents gave detailed information on how compensating a participant improved the retention and recruitment rate. Principal investigators stated that the compensation shouldn't be to attract participants. Participants must be reimbursed for their transport and time. The amount must be approved by the ethics committee.

> *"Mamalel" (to make it too attractive) is not allowed. What we believe in is patients' needs to get reimbursed for their expenses and at the same time patients need to get beyond the reimbursement is getting compensation for their time… (PI 001)*
>
> *…compensation is one strategy for assisting the whole process of you to know recruitment and retention… (PI 016)*

6. Discussion

6.1 Overview of findings

This study aimed to explore the viewpoints of principal investigators, trial coordinators, trial nurses, trial physicians, and trial participants on challenges and strategies for recruitment and retention of participants in clinical trials.

6.2 Challenges and strategies for recruitment and retention of trial participants

Study respondents identified factors related to study design, particularly clinical trial team factors, participant factors, and study factors to be important challenges. They also recognized five main strategies such as, promoting clinical trials, improving communication skills, and improve the system and a good estimation of cost were accounted to be key strategies to overcome those challenges for recruitment and retention.

Study respondents perceived that poor communication skills, lack of knowledge about research, low education level, and long questionnaires/assessment tools were the most common challenges for the recruitment of participants. Similar studies were done on the challenges and strategies of recruitment in other countries. In our study, poor communication skills and lack of knowledge of the trial team were found to be the main factors affecting recruitment. One of the previous studies found out that trial physicians were not always aware of existing clinical trials and the complexity of information sheets and consenting forms for trial participants with low-level education may also be a challenge (8). Respondents perceived that many potential trial participants had biased information about clinical trials. Individuals may get negative information from the public or media. Studies showed that negative information delivered through media unpleasantly affected the attitude and belief of the community towards clinical trial research (4, 17). It was stated that stringent eligibility criteria were responsible for the low recruitment and retention of trial participants. This finding is in agreement with that of a previous study that found that strict inclusion and exclusion criteria were accountable for the recruitment process (19).

Some studies stated that a poor choice of study site will be a big challenge for recruitment and it showed the importance of appropriate site selection and training as overall successful strategies

for recruitment (19-20, 42). Other studies recommended that the budget to train recruitment staff should be made available prior to the commencement of trials (6, 11, 13, 17, and 23). Respondents stressed that a trained and qualified clinical trial team was important to meet recruitment and retention goals. The clinical trial team is the one who communicates information with potential participants and establishes a good relationship with them, and the communication method, as well as communication skills, determines whether the participants have an interest in the study or not. According to a study conducted in Australia, Melbourne revealed that media was the easiest way of conveying information and addressing more people within a short time (18). As well as research conducted in India showed that media can play a major role by providing data on the significance of conducting clinical trials, how they contribute to new drug development, how potential participants play a key role in this process of new drug development by engaging themselves to the clinical trials. However, sometimes the negative data provided by the media may badly affect the opinion and attitude of the community towards clinical research (4). Media surely facilitates the recruitment process, though our findings suggest that using media outlets was not feasible in Ethiopian settings. Most of the respondents explained that society did not have access to technology. It was also noted that there was a trust issue, poor awareness, and low knowledge among the community as there was poor reading culture. The advertisement might be misleading if not well communicated, and potential participants might misunderstand the information.

Also, most respondents mentioned the importance of raising awareness among the community and health professionals. This finding in agreement with that of an earlier study which indicated that creating awareness in the community and health professionals on the existing clinical trials is very useful to improve recruitment (18). Also, respondents noted that a positive approach is a key strategy to recruitment: this was also identified in many kinds of research which emphasized that the clinical trial team needed to be good communicators and have a flexible and positive approach towards trial participants (43). Moreover, some respondents indicated that the referral system is one of the strategies to enhance recruitment. They thought that participants are tending to have an interest in the trial while they were endorsed by their physicians. Studies also showed that sensitizing sources of referrals to the trial helped to increase recruitment (23-24).

It was also noted that demanding participants much like frequent appointment schedules, subjecting to uncomfortable procedures and long waiting time was the main factor for high attrition

rate. This is in agreement with the finding of a previous study which stated that clinical trials should be as convenient as possible was since participating in trials should be voluntary (22). Also earlier research in Baltimore, US has shown that high study demands such as frequent appointments, long study periods, and painful procedures, travel costs may discourage participants from staying in the research (17). Few respondents also recognized many similar participants related challenges to retention that has been distinguished in the literature. However, some significant differences were also seen. They stated that the low education level among trial participants is one of the challenges they faced. Trial participants have difficulty understanding the concept of clinical trials and this leads to miscommunication and they were failed to stay long in the study. A previous report from the US revealed that lower education level is one of the factors to discourage participants from remaining in the research (9). One challenge was also noted by respondents that are not widely reported in the literature. Respondents mentioned that participants are tending to change their home addresses or job more frequently and are moving to new places to look for new houses or jobs. Changing the area is an increasing challenge to trial participants completing the trial periods. The other participant challenge is the lack of social support. Many of the respondents explained that trial participant's families are not happy for their siblings to be part of the study. Through the study period, participants failed to complete the study because the negative pressure from their families is very serious. One research in New York, US showed that lack of social support one of the challenges for participants to drop out of the trial (9).

The inability to keep participants until the study closes out will introduce bias and reduce the study power (29). Our finding showed that compassionate respectful care was the most important strategy to retain participants until the study closes out. This finding is in agreement with that of a previous study in London which emphasized that participants have to be compensated for the time taken to participate and transport expenses as part of compassionate respectful care (6, 28). Caution, however, must be taken to avoid undue inducement while compensating participants. Respondents also reported that providing clear and detailed information about the trial will help potential participants to come up with sound decisions to stay in the study. Previous research also supported this strategy. According to Idoko et al. stated that adequate clarification of trial processes and risk/benefits will enhance the retention of participants (42). In addition, respondents distinguished that establishing an efficient tracing system is one of the important strategies to retain participants. This strategy is widely reported in many types of research which elucidated that

retention relies on being able to trace study participants. Participants are asked to give telephone and home addresses to contact them to check their health progress, remind appointments, and whenever they missed visits (9). Also, some respondents identified flexible management of participants is one of the strategies they are using to increase retention. This finding was also described in earlier research in the United Kingdom which stated that more convenient follow-up dates and reducing the burden of follow up for participants were thought to be more effective for retention (43). Thus, the good management of participants had a significant impact on the study. Also establishing a community advisory board is one of the techniques most mentioned by the respondents. They stressed that it has a positive impact on retention. This finding is cited in many kinds of research that give details on the involvement of community leaders. Engaging community leaders was vital to acquisition community acceptance of the clinical trial also the community advisory board helped to clear out a negative rumor that was circulating in the community (42).

To conclude, this study finding demonstrates major challenges and for recruitment and retention of trial participants. Poor communication skills and lack of knowledge about existing trials were accounted to be major clinical trial team factors. In addition, misconceptions about the trial, low-level education, and lack of social support were revealed to be an important challenge among trial participants. Also, study factors such as long questionnaires and assessment, stringent eligibility criteria, extra, and inconvenient procedures were recognized as the main challenges. However, a wide range of strategies was identified such as increasing awareness, choosing an appropriate trial site, developing rapport, reimbursement, and establishing an efficient tracking system may be the most important intervention to improve recruitment and retention.

6.3 Strengths and limitations of the present study

This qualitative study had many strengths and limitations. This is the first kind of study conducted on challenges and strategies for recruitment and retention of trial participants in Ethiopia. One of the strengths of the present study is that the findings provide views of different stakeholders such as principal investigators, trial coordinators, trial nurses, trial physicians, and trial participants. The second strength was that it involved purposive sampling to reveal a comprehensive variety of information. The third strength was that the study employed respondents with reach experiences in clinical trials for 5-10 years. The fourth strength was that the interview questions were open-

ended and additional comments were entertained so that they allowed participants to tell whatever they felt without restriction.

The limitations include enrolling few (only 3) respondents who were trial participants, short participant's interviews which might have limited the amount of information to be obtained; and not been able to make a meaningful comparison on trial participants from Jimma and Gondar study sites as a result of country instability and COVID-19 pandemic.

7. Conclusions

This is the first study of its kind in Ethiopia. Findings from this study can inform potential strategies to improve recruitment and retention of participants in clinical trials from the perspectives of Ethiopia clinical trial principal investigators, trial nurses, coordinators, physicians, and participants. From the present study, it can be concluded that lack of knowledge and high study demand were the main challenges for participants recruitment and retention, respectively; and creating awareness of potential participants on clinical trials and compassionate respectful care are key strategies to improve trial participants' recruitment and retention, respectively to meet trials' objectives successfully. Moreover, community engagement can also improve both recruitment and retention of trial participants.

Finally, Identifying potential challenges for recruitment and retention of trial participants will be useful to develop recruitment and retention plans in advance. Likewise, it helps to address possible challenges ahead as well as will improve the recruitment and retention of trial participants. This leads to a successful trial.

8. Recommendations

- Recruitment and retention involve collaborative determinations from all affiliates of the clinical trial team along with trial sponsors. Both are dependent on organizational support, and the approach of the clinical team. In addition, principal investigators themselves need to be diligent, have professional integrity, plan precisely, and develop good interpersonal skills.
- Promoting compassionate respectful care can help to establish trust and rapport with trial participants, therefore; better participant retention would be achieved. Providing sufficient, clear, and brief explanations about trial procedures and assessment to trial participants during the consenting process also assist participant retention.
- Research related challenges can be prevented if recruitment goals, eligibility criteria, and study procedures are adequately discussed by both the principal investigator and sponsor during the feasibility trial period. Furthermore, Principal investigators need to adequately allocate resources in terms of human power as well as infrastructure.
- Appropriate training of the trial team on recruitment and retention strategies may also enhance the recruitment and retention rate. Strategies should be a focus on solving common biased information about clinical trials. It should also involve community awareness of clinical trials; this may enhance the interest of participants to be part of the clinical trials. It is also recommended that the testimonials of potential participants by their physicians may improve trial participation.
- The problem of the negative view of clinical trials in Ethiopia needs to be addressed by conveying a wide range of education in the field of clinical trials, ethics, and regulations to mass media as well as the general public. This can be attained by creativities such as establishing health education programs, issuing enlightening articles about clinical research, developing informational posters that can be exhibited in hospital wards.
- It is recommended that early retention strategies should be integrated into recruitment strategies during the planning phase of the trial. Strategies like effective, persistent, and clear communication with trial participants, emphasis on the effective consenting process along a good relationship with trial participants may encourage retention.
- It is also recommended that further study has to be done to explore other challenges and strategies in different clinical trial sites in Ethiopia.

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Appendix I: Key Stakeholder Interview Guide

The following is an interview guide, which will be used with interviewees to guide the interview process. It contains the Interview objective, Information sheets, a Consent form, and a set of questions.

Interview Objective

- To identify and understand the challenges and strategies for recruitment and retention of participants in clinical trials in Ethiopia. A Qualitative Study

Participants Selection criteria

- Principal investigators, clinical coordinators, trial nurses, and trial physicians who are currently working or had worked in clinical trials research in Ethiopia specifically in Armauer Hansen Research Institute, Addis Ababa University/College of Health Sciences, Jimma University Teaching Hospital, University of Gondar, and Zewditu Memorial Hospital.

Appendix II: Information sheet

Title of the study: ***Challenges and Strategies for Recruitment and Retention of Participants in Clinical Trial in Ethiopia: A Qualitative Study***

I would like to thank you for taking the time to meet today, your contribution is greatly valued. My name is **Lealem Minwuyelet Wagaw**, professionally a Nurse, pursuing an M.Sc. degree in Clinical Trials at Addis Ababa University CDT-Africa. Currently, I am collecting data for a research project intended to identify ***Challenges*** **and Strategies for the Recruitment and Retention of Participants in Clinical Trials in Ethiopia.**

I will interview you about your experiences in conducting clinical trials related to challenges and strategies for recruitment and retention of participants in clinical trials to capture lessons for future interventions.

Participation in this research is purely voluntary and you may withdraw from the research at any time without giving a reason, and with no consequences. I will be taking notes and using a tape recorder not to miss any comments. Please note that the **CONFIDENTIALITY** of your responses is meticulously assured. All the responses you provide are anonymous; it will only be shared with the research team. We will ensure that any information includes in our report does not identify one as a respondent. If one does not want to respond to any of the questions, he/she is not obliged to do so. If you have any questions do not hesitate to ask.

Feel free to contact me if you have any inquiry by the following address:

Tel:- ***+251-947-33-92-72/ +25138191219***
Email: lealemminwuyelet@gmail.com / lealem_minwuyelet@slu.edu.et

- This form will be filled and signed in two copies.

Thank you very much!

I agree to participate in this study (Tick **"✓"**) ☐

Participant's Code: _____ Signature of participant's: _____ Date: ___/___/2020

Appendix III: Consent form

Dear participant, please **tick every box** to show agreement on each point and sign the consent sheets at the end of this form. If there is any unclear point, do not hesitate to ask.

No.	Items	Tick Box☑
1.	The study has been explained in a language that I comprehend. All the questions I had about the study have been answered. I understand the interview and what is expected.	☐
2.	I understand the confidentiality of personal information is guaranteed. The information during the interview will remain completely confidential.	☐
3.	I understand being participation in this study is voluntary and the right to withdraw from this interview/study without giving a reason.	☐
4.	It is explained that sometimes the researchers find it helpful to use their own words when writing up the findings of the research. I understand any use of words would be completely anonymous (without my name).	☐
5.	I understand information collected is confidential, and it will be reported without personal information with one's approval.	☐
➢ This form will be filled and signed in two copies.		

I understand all the information given above and agreed to participate in this study by interest.
Participant's Code: _____

Signature of participant's: _____ **Date:** ___/___/2020

Appendix IV: Questions and Closing key Components

Background	1. Gender (1) Male (2) Female 2. Academic background _____ 3. Profession _____ 4. Year of working experience _____ 5. Clinical trial experience years _____
Topic I (Challenges and Strategies for Recruitment of clinical trials participants)	1. What is patient recruitment in clinical trials? 2. How do you recruit participants for a study? 3. Which strategies/practices do you use routinely to improve recruitment? 4. Do you consider the areas in which you conduct research while you develop a recruitment plan? 5. Which strategies/practices to improve recruitment have you evaluated? a. Please give the details of the following: situation prompting action, method of evaluation, the involvement of ethics committee, effect/results, and impact on your work. 6. Concerning to improve recruitment, is there anything else that would influence your future practice that you have not described above? 7. What do you remark to be challenging for recruitment interventions? 8. Do you actively set specific goals for the recruitment of participants in clinical trials? 9. Do staff members who is working in the recruitment taking training prior to the recruitment process?
Topic II (Challenges and Strategies for Retention of clinical trials participants)	10. What is participant retention in clinical trials? 11. What are the best approaches (from personal experience) for designing and communicating information about trial retention for trial participants? 12. Which strategies/practices do you employ routinely to ensure participant retention better? 13. What strategies (e.g. sending gifts or saying 'thank you') make participants feel valued and how do they affect retention? 14. What are the best strategies for using participant incentives (e.g. monetary or non-monetary), and how should they be implemented (e.g. when should they be provided) when collecting information from participants in clinical trials? 15. What behaviors' of trial staff (e.g. being friendly) result in improved retention? 16. Which strategies/practices to improve retention have you evaluated? 17. Concerning to improve retention, is there anything else that would influence your future practice that you have not described above? 18. What are the challenges of retention? 19. What aspects of trial retention do participants perceive as burdensome, and how can these be addressed?

	20. What is the impact of timing, frequency, and duration of follow-up (e.g. questionnaires, clinic appointments) on retention? 21. What influence does the relationship between trial staff and participants have on retention? 22. Have you adjusted your research to be more inclusive? 23. What aspects of trial recruitment processes could be changed to improve retention?
Topic III (Closing Key Components) • Additional comments • Thank you	• These are the questions I had for you. Is there anything more you would like to add? • Your patience and co-operation are truly appreciated. I will be in touch if anything comes up for which I might need your expert views. I will be available if you need to contact me for any reason related to this interview. **Thank You!**