ADDIS ABABA UNIVERSITY

INVESTIGATING RESEARCHERS' PERCEPTIONS AND EXPERIENCES IN CONDUCTING CLINICAL TRIALS TOWARD ZOONOTIC DISEASES IN ETHIOPIA

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Investigating researchers' perceptions and experiences in conducting clinical trials toward zoonotic diseases in Ethiopia

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DECLARATION

I, the undersigned, declare that this thesis (research work) entitled “Investigating researchers’ perceptions and experiences on conducting clinical trials towards zoonotic diseases in Ethiopia” is my original work and has not been presented in any other university or organization and that all sources of materials used for the thesis have been duly acknowledged.

Declared by:

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Date: June 2020

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LIST OF ACRONYMS/LIST OF ABBREVATIONS

AHRI	Armauer Hansen Research Institute
AI	Avian Influenza
CDC	Centers for Disease Control and Prevention
CDT-Africa	Center for Innovative Drug Development and Therapeutic Trial for Africa
CFR	Case Fatality Rate
CFT	Complement Fixation Test
ELISA	Enzyme-Linked Immunosorbent Assay
EPHI	Ethiopian Public Health Institute
EWA	Ethiopian Wildlife Authority
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HPAI	Highly Pathogenic Avian Influenza
NAHDIC	National Animal Health Diagnostic and Investigation Center
NVI	National Veterinary Institute
OHZDP	One Health Zoonotic Disease Prioritization
PEP	Post Exposure Prophylaxis
RBPT	Rose Bengal Plate Test
RNA	Ribonucleic acid
RVF	Rift Valley Fever
WHO	World Health Organization

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ABSTRACT

Background: The emergence and resurgence of zoonotic diseases have continued to be a major threat to global health and the economy. Developing countries are particularly vulnerable due to agricultural expansions and domestication of animals with humans. Scientifically sound clinical trials are important to find better ways to prevent, diagnose, and treat zoonotic diseases, while there is a lack of evidence to inform the clinical trials' capacity and practice in countries highly affected with the diseases. This study aimed to investigate researchers' perceptions and experiences in conducting clinical trials towards zoonotic diseases in Ethiopia.

Methods: This study employed a descriptive, qualitative study design. It included major academic and research institutions in Ethiopia that had active engagements in veterinary and public health researches. It included the National Veterinary Institute, the National Animal Health Diagnostic and Investigation Center, the College of Veterinary Medicine at Addis Ababa University, the Ethiopian Public Health Institute, the Armauer Hansen Research Institute, and the College of Health Sciences at Addis Ababa University. In-depth interviews were conducted with 14 senior research investigators in the institutions who hold a proven exhibit primarily leading research activities or research units. Data were collected from October 2019 to April 2020. Data analysis was undertaken using open code 4.03 for qualitative data analysis.

Results: Five major themes, with 18 sub-themes, emerged from the in-depth interviews in connection with. These were: challenges in the prevention, control, and treatment of zoonotic diseases; One Health approach to mitigate zoonotic diseases; personal and institutional experiences in conducting clinical trials on zoonotic diseases; barriers in conducting clinical trials towards zoonotic diseases; and strategies that promote conducting clinical trials on zoonotic diseases. Conducting clinical trials on zoonotic diseases in Ethiopia is hampered by a lack of clearly articulated ethics and regulatory frameworks, trial experts, financial resources, and good governance.

Conclusions: In Ethiopia, conducting clinical trials on zoonotic diseases deserves due attention. Strengthening institutional and human resources capacity is a precondition to harness effective implementation of clinical trials on zoonotic diseases in the country. In Ethiopia where skilled human resource is scarce, One Health approach has the potential to

form multidisciplinary teams to systematically improve clinical trials capacity and outcomes in the country.

Keywords*:* clinical trial, zoonotic diseases, Ethiopia.

1. INTRODUCTION

1.1.Background

Zoonotic diseases are diseases that are transmissible between animals (domestic and wildlife) and humans (1). The word 'zoonosis' (plural: zoonoses) was introduced in 1880 by Rudolf Virchow to collectively include the diseases shared in nature by animals and humans. Later, in 1959 WHO defined Zoonoses as "those diseases and infections which are naturally transmitted between vertebrate animals and humans (2). Zoonoses constitute a diverse group of viral, bacterial, rickettsial, fungal, parasitic, and prion diseases (3). These diseases have a different way of transmission mechanisms that may be direct with diseased individuals and an inanimate object such as in rabies and anthrax or indirect, via vectors, food, water, and the environment, as in the case of bovine tuberculosis, leptospirosis, and echinococcosis. Many, such as brucellosis, also have multiple routes of infection (1).

The importance of zoonotic diseases has increased at global and regional levels in recent years in connection with human population growth, intensive human and wildlife migration, urbanization, increased international travel and trade of animals and products of animal origin, and intensification of animal production. Many of the human diseases that are new, emerging, and re-emerging are caused by pathogens that originate in animals or products of animal origin. The development of antimicrobial resistance poses an increasing burden on health care systems in the treatment of some zoonotic diseases (4). Developing countries have a higher incidence and prevalence of zoonoses, and this is attributed to the lack of adequate control mechanisms, inadequate infrastructure, and lack of adequate information on their significance and distribution (5).

In Africa, Ethiopia has the second largest human population and the largest livestock population (6) and is particularly vulnerable to the effects of zoonotic diseases because the economy is largely dependent on agriculture (7) and roughly 80% of households have direct contact with domestic animals, that favour an opportunity for infection and spread of disease (8). Ethiopia also ranks very high in the health burden of zoonotic diseases and in having a large population of poor livestock keepers (6). Since a large number of zoonotic diseases endemically arise in Ethiopia, a prioritization process was essential to categorize the most serious zoonotic diseases that should be co-operatively addressed by animal and public health agencies to exploit the impact on the health of people and animals. The zoonotic diseases

prioritization workshop that was conducted in Ethiopia from September 25-26, 2019 guided a range of government agencies through the process to prioritize zoonotic diseases of greatest concern for Ethiopia and develop next steps and action plans to address the priority zoonotic diseases in collaboration with one health partners. In the prioritization process, potential zoonotic diseases of concern were identified through a set of criteria. As a result of the prioritization process, human and animal health agencies co-operatively identified five zoonotic diseases they can jointly start to tackle. These are rabies, anthrax, brucellosis, Rift Valley fever, and zoonotic avian influenza (9).

Control of zoonotic diseases constitutes an important health matter. However, many factors involved in the prevention and control of zoonotic infections cannot be addressed by public health sectors only. Success in reducing the public health significance of zoonotic diseases greatly depends on the level of cooperation between public and veterinary health sectors using one health approach in the diagnosis of zoonoses, exchange of information, organization of shared surveillance systems, common training of staff and creation of community awareness. High-level commitment and the ability of national programmers to mobilize the necessary resources and to collaborate closely with other relevant sectors are needed to cope with the common challenges. Moreover conducting clinical trials towards zoonotic diseases is paramount to reduce the impact on animal and human health (10).

Clinical trials are scientific studies conducted to find better ways to prevent, screen, diagnose or treat diseases. Diagnostic trials are aspect of new or improved methods for diagnosing a certain disease or condition, interventional clinical trials are assessment of the safety and efficacy of an experimental treatment in a randomized controlled clinical trial. Observational clinical trials are studies of diseases or general health status in populations where they naturally happen, prevention trials are test approaches for preventing the occurrences or recurrences of diseases. Methods could include medical treatment, diet and lifestyle changes, dietary supplements, exercise, and vaccines, quality of life or supportive care trials that look for ways to improve the quality of life for individuals with a chronic illness, treatment trials that test new medical, surgical, and/or radiation treatments for combating illness, screening trials that look for new or improved ways to detect a particular disease or condition. The designs of clinical trials are critical to ensuring the scientific validity and reproducibility of the results (11). In Ethiopia, the number of clinical trials that have been done keeps growing throughout the years. However, compared to other countries, it is still much lower. Ethiopia

shares only 2.2% of clinical trials generated out of Africa (11). This is due to the existence of many challenges for the conduct of clinical trials that would determine the safety and efficacy of new products and interventions in the country. Due to this, there are few tendencies to conduct clinical trials towards zoonotic disease. Thus this study intended to investigate researchers' perceptions and experiences on conducting clinical trials towards zoonotic diseases in Ethiopia.

1.2.Statement of the problem

Globally, an estimated 60–70% of emerging infectious diseases in humans are zoonotic in nature. Developing countries have a higher incidence and prevalence of zoonoses, and this is attributed to the fact that animals and people often live close together. People are especially dependent on livestock and poultry for food, clothing, fertilizer, draught power, and, to an important degree, financial security. Livestock producers are at risk and more frequently acquire these infections from their animals (2). At least, 55 000 people die of rabies in Asia and Africa per annum, and expenses related to the prevention and control of this disease in the two continents is estimated at US$ 590 million. Brucellosis remains one of the most common zoonotic diseases worldwide with more than 50,000 human cases reported annually (5). Several zoonotic diseases endemically occur in Ethiopia. The zoonotic diseases prioritization workshop conducted in Ethiopia from September 25-26, 2019 guided a range of government agencies through the process to prioritize zoonotic diseases of greatest concern for Ethiopia and develop next steps and action plans to address the priority zoonotic diseases in collaboration with One Health partners. In the prioritization process, potential zoonotic diseases of concern were identified through a set of criteria. As a result of the prioritization process, human and animal health agencies co-operatively identified five zoonotic diseases they can jointly be tackled. These are rabies, anthrax, brucellosis, Rift Valley fever, and zoonotic avian influenza. Although zoonotic diseases have been investigated in Ethiopia, much of the research focused on epidemiology, socio-economic impact, and knowledge, attitude, and practices. So far, there are few studies in Ethiopia supported with sufficient and concrete data on prevention and control of zoonotic diseases including conducting a clinical trial. Moreover, no study has so far been conducted to investigate researchers' perceptions and experiences in conducting clinical trials towards zoonotic diseases in Ethiopia.

2. RESEARCH QUESTIONS

Based on the gap in knowledge identified, the study was entirely focused on finding answers for the following basic questions:

1. What are the perceptions of researchers concerning challenges of prevention, control, and treatment of zoonotic diseases
2. What are the perceptions of researchers in conducting clinical trials towards zoonotic diseases?
3. What are the experiences of researchers in conducting clinical trials towards zoonotic diseases?
4. How do animal and public health researchers work together using one health approach regarding conducting a clinical trial for zoonotic disease? What is done so far?
5. What are the major challenges encountered in conducting clinical trials towards zoonotic diseases?

3. LITERATURE REVIEW

3.1.Overview of zoonotic diseases

Historically, zoonotic diseases had a remarkable influence on the evolution of man, particularly those cultures and societies that domesticated and farmed animals for food and clothing. Zoonoses occur throughout the world transcending natural boundaries. Economy and health are well known, extending from the international movement of animals and importation of diseases to bans on the importation of all animal products and restrictions on other international trade practices. Over the last two decades, there has been a significant change in the importance of some zoonotic diseases in many parts of the world, occasioning from ecological changes such as urbanization, industrialization, and the diminishing proportion of persons working in the so-called primary sector (1).

From those zoonoses recognized today as predominantly important are brucellosis, bovine tuberculosis, anthrax, plague, leptospirosis, salmonellosis, rabies, several common arthropod born viral infections (arboviral infection), certain parasitic diseases, especially cysticercosis, hydatid disease, trypanosomiasis, and toxoplasmosis. With advanced laboratory techniques and increased awareness among medical and veterinary scientists, ecologists, and biologists, more than 300 zoonoses of diverse etiology are now recognized (4).

Zoonotic diseases are classified according to the etiological agents, bacterial zoonoses, viral zoonoses, protozoal zoonoses, Helminthic zoonoses, fungal diseases, and ectoparasites infestations. Zoonotic diseases are transmitted directly from an infected vertebrate host to a susceptible host (man), indirectly by contact with a fomite, or by the bite of a vector (4).

The importance of zoonotic diseases has increased at global and regional levels in recent years in connection with human population growth, intensive human and wildlife migration, urbanization, increased international travel and trade of animals and products of animal origin, and intensification of animal production. Many of the human diseases that are new, emerging, and re-emerging are caused by pathogens that originate in animals or products of animal origin. The development of antimicrobial resistance poses an increasing burden on health care systems in the treatment of some zoonotic diseases. The public health significance of zoonotic diseases is growing in the developing country. In addition to causing human

morbidity and mortality, such diseases hamper agricultural production, decrease the availability of food, and create barriers to international trade (5).

Zoonotic diseases can threaten human health in different ways: endemic zoonoses are continually present to a greater or lesser degree in certain populations. They are common in poor populations and are responsible for around a billion illnesses and millions of deaths every year. However, endemic zoonoses have been neglected by the international donor, standard-setting, and research communities (12). An outbreak of epidemic zoonoses typically occurs intermittently. Endemic zoonoses may occur as outbreaks in naïve populations or when triggered by events such as climate changes, flooding, waning immunity, or concomitant disease. They typically have high temporal and spatial variability. Emerging zoonoses newly appear in a population or have existed previously but are now rapidly increasing in incidence or geographical range. Old zoonoses were originally zoonotic but are now spreading mainly or entirely by human-to-human transmission (some with remaining zoonotic reservoirs (2).

3.2.Priority zoonotic disease in Ethiopia

One Health Zoonotic Disease Prioritization (OHZDP) Workshop in Ethiopia was conducted in Addis Ababa from 25-26 September 2019. The goals of the OHZDP workshop were to use a multisectoral, one health approach to prioritize zoonotic diseases of greatest concern for Ethiopia and develop next steps and action plans to address the priority zoonotic diseases in association with one health partners. As a result of this, OHZDP process brought together representatives from animal, human and environmental health sectors (organizations), as well as other important partners, to prioritize zoonotic diseases of utmost concern for multisectoral, one health partnership. This process used a transparent method and integrated equal input from the ministries representing one health sectors working at the human, animal and environment interface, namely the Ministry of Health which represented by the Ethiopian Public Health Institute (EPHI), The Ministry of Agriculture, the Ministry of Culture and Tourism, represented by Ethiopian Wildlife Authority (EWCA), and the Ministry of Environment, Forest and Climate Change. This prioritization process developed locally appropriate criteria and that can address the needs of each unique location to prioritize the list of zoonotic diseases, developed a categorical question to measure each criterion and prioritize zoonotic diseases. It scored each zoonotic disease by answering the categorical questions for each weighted criterion and entering this data into the OHZDP tool. After going through the

above-mentioned process, the final top five Ethiopian priority zoonotic diseases identified were anthrax, rabies, brucellosis, Rift valley fever, and zoonotic avian influenza (9).

Anthrax is an acute, almost always fatal zoonotic disease caused by spore-forming bacteria called Bacillus anthracis. Predominantly, anthrax causes disease in herbivores such as cattle, goats, and sheep. In animals, the disease is contracted from contaminated pasture and humans get infected through contact or the food chain directly from animals, the environment, and fomites (13). There are three main clinical forms of anthrax. These are inhalational, gastrointestinal and cutaneous. Cutaneous anthrax is the most common form accounting for about 95% of the cases and it commonly occurs in bare skin areas, like the forearms, face, neck, and. on the other hand, a more serious form is the inhalation anthrax with a mortality rate of up to 100% (29). Generally, The disease is characterized by septicemia and sudden death with exudation of tarry blood from anybody's body orifices of the cadaver, Failure of the blood to clot, the absence of rigor mortis and the presence of splenomegaly are the most important necropsy findings of the disease (13). Since farmers, butchers, veterinarians, shepherds, and farmworkers are at great risk of exposure to infected material, the disease is considered as an occupational disease usually limited to developing countries. It is, therefore, a common disease in parts of Africa, Latin America, Asia, and Eastern Europe (29). However, in the developed nation, the incidence of anthrax had become a concern, for example in the U.S during the early 1900s where approximately 130 human cases occurred annually, but now only one or two cases are generally seen in a year. However, in developing countries(29), anthrax is still a significant risk and outbreaks occasionally occur in humans.

In Africa, estimates suggest that each animal with anthrax can result in up to ten human cases (29). In Ethiopia, anthrax is an endemic disease which occurs in May and June every year (seasonal occurrence). It is an important public health issue. although suspected cases of livestock anthrax are reported from several districts, few of those are officially confirmed (29).

Rabies is a highly fatal neurotropic zoonotic disease of all warm-blooded animals including humans. It is caused by the rabies virus, which belongs to the genus Lyssavirus in the family Rhabdoviridae (19). The disease spreads through a bite from an infected animal, and humans get infected when bitten by an infected animal or contact with the saliva of an infected animal and then the virus will migrate to the brain. More than 94% of human cases are occurring due to a bite from a rabid dog, since domestic dogs are the most important sources of infection

(12). This disease is one of the public health concerns around the globe because of its high fatality zoonotic nature among animals and humans. It has been classified as the eleventh killer disease in the world, killing 60 - 100, 000 human beings annually (12). The occurrence of rabies is very high in developing countries of African and Asian continents,55% in Asia, and 44% in Africa (22). Many studies have been undertaken in different regions of Africa including Ethiopia to implement a rabies control program. These studies highlight that dogs are very important particularly stray dogs in the transmission of rabies to humans (15).

In Ethiopia, rabies is an endemic zoonotic disease and is one of the high burdened countries were 10,000 people per annum were estimated to have died (24) and in the world rabies survey report, it was found to be the second leading country. In 2012, over 1400 deaths were estimated to occur in the country due to rabies annually (25) and a very recent global burden estimate reported that over 2700 human lives are lost in the country annually (26). The current scenario in Ethiopia shows primarily a serious threat of canine rabies virus transmission in the rapidly growing human population in which a poorly controlled stray dog population is equally growing fast (27).

Brucellosis is one of the most common re-emerging zoonotic diseases worldwide and caused by small coccobacilli bacteria of the genus Brucella, which affects domestic animals, wildlife and humans. It is transmitted to humans through the consumption of unpasteurized dairy products and uncooked meat (28). The most common species mainly known in livestock are *B. abortus, B. melitensis, B. suis, B. canis, and B. Ovis* (39). Clinically, the disease is characterized by reproductive problems such as abortion, infertility, and low milk yields, death from acute metritis, sterility, arthritis or bursitis (hygroma), and increased cost of animal replacement as well as lowered sale value of infected animals and loss in international trade, and human, it is characterized by fever, fatigue, sweating, joint pain, headache, loss of appetite, muscular pain, lumbar pain, weight loss and arthritis (39). Globally, about 500,000 new cases are reported annually, with prevalence rates in some countries exceeding 10 cases per 100,000 population (39). Even though there is a high burden of infection in many areas of the world, brucellosis is rarely prioritized by health systems and is considered a neglected zoonosis by the World Health Organization (WHO) and World Organization for Animal Health (OIE) (32).

As brucellosis is an endemic disease across much of sub-Saharan Africa, with a varying degree of prevalence between production systems, the economic and public health impact remains a concern in developing countries (43). Several studies have been carried out on brucellosis in Ethiopia, with reports of varying prevalence rates.

Rift Valley fever (RVF) is an emerging trans-boundary, mosquito-borne, zoonotic viral disease caused by a single-stranded RNA virus that belongs to the genus Phlebovirus. It is considered an important threat to both animal and public health in African and Middle Eastern countries. The utmost susceptible hosts to RVF infection are cattle, buffaloes, goats, sheep, and some wild animals. Morbidity and mortality rates vary according to the age and the species of animals. The mortality rate ranged from 80% to 100% in young animals. In young animals, the disease is related to ultimately death, fever, and anorexia while in adult animals, it differs from in-apparent form to acute form and is characterized by fever, bloody diarrhea, vomiting, and weakness (34).

RVF virus is transmitted to humans through drinking unpasteurized milk, direct contact with infected animal's blood, aerosol, or the bite of infected mosquitoes. Aedes and Culex mosquitoes are considered the main vectors. The disease in humans differs from influenza-like illness to more complicated forms such as renal failure, hemorrhagic fever, retinitis and, encephalitis. Notably, RVF outbreaks are episodic and associated with climatic, hydrologic, and socioeconomic factors (34). RVF outbreaks have been reported in different countries, which were characterized by severe infection and death in humans, with a high case-fatality rate (CFR), 50% for the hemorrhagic syndrome form. East African outbreaks in Tanzania, Kenya and Somalia caused 309 human deaths in 2014 (61).

Avian influenza (AI) is an infectious disease of birds caused by type A influenza viruses, the family of *Orthomyxoviridae* . Three types of influenza viruses are identified. All those types can affect domestic animals like poultry, horses, pigs, etc., belong to type A which is the most common virus type producing serious epidemics in humans. Those viruses most commonly infect poultry as well as many types of wild birds. Some AI viruses are also known to infect a variety of mammals including humans. AI virus subtypes are identified by the neuraminidase antigens (glycoproteins) and haemagglutinin that cover the virus surface. nine different neuraminidase (N1-N9) and Sixteen different haemagglutinin (H1-H16) antigens have been characterized, and each viral subtype is distinguished by the particular

antigen combination it possesses e.g. H5N1 or H3N2. All 16 haemagglutinin and nine neuraminidase antigens have been existing in wild bird populations (35). Avian influenza infections may produce a mild disease revealed by a diversity of respiratory, enteric, or reproductive signs (depending on the strain). Clinical signs may include decreases in activity, food consumption or egg production, onset of coughing and sneezing, ruffled feathers, diarrhea, and/or tremors. At times, few visible clinical signs are noted and without specific laboratory testing, some outbreaks may go entirely undetected. Human infections can concur through direct contact with infected animals or contaminated environments. Infection of humans by A (H5) or A (H7N9) avian influenza viruses has an aggressive clinical symptom. Initial symptoms are high fever (≥ 39°C) and cough. Dyspnea is also a sign and symptom of the lower respiratory tract. Sore throat or coryza is a less common symptom of the upper respiratory tract. Other symptoms such as diarrhea, vomiting, abdominal pain, bleeding from the nose or gums, and chest pain have also been reported in some patients. Complications of infection include hypoxemia, multiple organ dysfunction, and secondary bacterial and fungal infections. The high impact of avian flu (highly pathogenic avian influenza) (HPAI) requires policymakers to consider and put in place appropriate measures for disease surveillance and control systems, especially in developing countries, to control the spread of the disease (36).

3.3.Challenges and strategies in the control of zoonotic diseases in Ethiopia

Most of the zoonotic diseases are trans-boundary. They spread across boundaries from their origin, to influence on trade, tourism commerce, and consumer with devastating economic consequences. Many of the zoonoses outbreaks have occurred in remote areas, making it impossible to deliver public health services to these hard-to-reach populations (37). In Ethiopia, the detection and diagnosis of the diseases have been significantly hindered due to difficulties in organizing teams of professionals, lack of proper laboratory diagnostic facilities and insufficient capacities to plan, mobilize and implement appropriate control measures in such settings and to monitor the progress of control measures in geographically dispersed areas (38).

Most pathogens that cause zoonotic infections in humans originated from animals or products of animal origin. Knowledge of extra-human reservoirs of these pathogens remains essential for understanding the epidemiology and potential control measures of these zoonotic diseases (7). However, in Ethiopia, due to lack of knowledge of these diseases, medical authorities in the country often deny the existence of human cases, making it difficult for these agencies to

understand the epidemiology, disease progression and use the opportunity to understand which methods work and which ones do not work for the control of these diseases in different settings (39). The major limitation in controlling the zoonotic infections in the country include lack of effective collaboration between the animal and human health sectors under the concept of "one health" approach, which links the human with the animal health sector integrating the animal and human disease surveillance and response system that could, otherwise, have helped in controlling zoonotic infections in animal reservoirs, enabling early outbreak detection, and preventing deadly epidemics and pandemics (40). Additional challenges on the prevention and control of zoonotic diseases in Ethiopia include weak surveillance and reporting systems and the limited capacity of laboratory for the diagnosis of zoonotic diseases. Research capacity at the local level is limited in the country due to lack of awareness and attitude, inadequate infrastructure and supplies, and skilled manpower. There is also a lack of institutionalized inter-sectoral collaboration mechanisms between the different sectors. There are difficulties in gaining accurate and recent information and reports on zoonotic disease conditions because of the incapability to obtain quality information and inadequate communication between Ministries of Health and Agriculture (veterinary services). There is also a lack of effective community participation and health education on zoonotic diseases in the country (10).

Research on zoonotic diseases is also limited particularly in clinical research. Low level of awareness among policy and decision-makers about the disease, inadequate information on the burden, trend and risks of zoonotic diseases, inadequate resources, lack of funding and skilled manpower for control of zoonotic diseases, presence of other competing health priorities often taking precedence are also the other challenges to prevent and control of zoonotic diseases in Ethiopia (10).

The main approach should start with developing a national plan involving all important stakeholders and sectors. The plan should reflect developing a geographic map of the distribution of zoonoses occurring in the country using geographic information systems and other information technologies, and conducting a detailed risk assessment. Furthermore, areas at risk for expansion of zoonosis should also be recognized. Considering the increasing importance of zoonotic diseases in the country, the most appropriate way would be to develop a strategic framework for the prevention and control/elimination of zoonotic diseases to minimize the health, social and economic impact of zoonotic diseases in the country. The

most significant and critical technical areas that will need to be considered are building effective collaboration between animal and human health sectors. Close collaboration between veterinary and public health specialists is important to enhance inter-personal and inter-organizational communication, improving surveillance for early detection of disease threats in humans (41).

4. METHODOLOGY

4. 1. Study area, design and period

The study which was conducted from October 2019 to April 2020 involved major veterinary and public health academic and research institutions that were selected using a purposive sampling approach. These included the College of Health Sciences (Addis Ababa University), Armauer Hansen Research Institute (AHRI), and the Ethiopian Public Health Institute (EPHI) from Addis Ababa, the capital city of the Federal Democratic Republic of Ethiopia. Addis Ababa is home to the African Union, Economic Commission for Africa, and international organizations. It is also the largest and the most populous city in the country with a total population of 3,384,569 according to the 2007 census (42). Other institutions involved in the study included College of Veterinary Medicine and Agriculture and National Veterinary Institute (NVI) from Bishoftu town located at 47.9 kilometers southeast of Addis Ababa (43) and National Animal Health Diagnostic and Investigation Center (NAHDIC) which is located in Sebeta town located at 19 kilometers west of Addis Ababa (43). In this research, the researcher has chosen a descriptive qualitative research design in the hope to explore researchers' perceptions and experiences in conducting clinical trials towards zoonotic diseases.

4. 2. Study Population

The researcher employed a purposive sampling method to recruit researchers from the selected study areas. The total number of participants in the study was 14. The researcher used data saturation criteria to determine the required number of participants. The selection of participants from every institution was facilitated by institution directors or deans. The inclusion criteria were being principal investigator or institution head/team leader or project coordinator or department head or senior researcher, having a minimum of three publications as the first author and/or minimum of 5-year work experience

4. 3. Sampling process

According to the legal procedure in the institutions, institutional directors, or college deans at each institution should first give verbal approval for a researcher to proceed to contact a participant. Therefore, after getting an approval letter for the study from the Addis Ababa University College of Health Science, CDT-Africa, the researcher contacted institutional directors or college deans at each institution to select the participants. All of the institutional directors or college deans received the letters and gave their verbal approval. Some recruited

the participants themselves based on the information they read in the letter, whereas others allowed the researcher to select by herself. Finally, the selected participants agreed and joined the study.

4. 4. Data Collection Instruments

Interview

In-depth, semi-structured qualitative interviews were conducted with researchers to explore the perceptions and experiences of conducting clinical trials towards zoonotic diseases. The investigator selected open-ended interviews as it allows participants to discuss their opinions, views, and experiences fully in detail as a set of interviews with closed-ended questions may perhaps inhibit participants from expressing their full opinions and feelings (44). For this purpose, the researcher prepared a list of questions to be responded with each participant. A face to face interview was conducted to allow the investigator to observe any non-verbal communication and both the interviewer and participant seek any clarification when necessary. All the interviews conducted during work hours in private rooms. The participants themselves scheduled when and where they were to be interviewed, and reported that they were comfortable about their decisions. The language of communication with the participants during the in-depth interviews was English. The investigator conducted an in-depth interview with two researchers to test the validity of the interview questions and gain experience in conducting an interview. When the investigator conducted in-depth interviews with all participants, she took some notes and audio-recorded the interviews for later transcription. The use of audio records determined by the participants' consent and each of them was asked whether they were comfortable with that. All agreed to be recorded except for two researchers who requested the investigator to take only notes while he/she spoke slowly. The interviews were consisting of nine open-ended questions, uniquely developed by the investigator for the sole purpose of this study (see Appendix II for sample interview guide)

4. 5. Data analysis and Interpretation

The researcher started analyzing the material during her fieldwork. This was done to detect gaps or a lack of information and, therefore, to produce a good description of topics through the interviews. The audio files from the in-depth interviews were then transcribed and data analysis was undertaken using open code 4.03 for qualitative data analysis. To improve the rigor of the study, two researchers were involved in the data analysis (SB and AA). Braun

and Clark's reflexive thematic analysis framework was used and the analysis process followed the six phases this framework suggests – familiarization, initial coding, theme construction, reviewing themes, defining themes, and producing the report (45). Having a number of codes helped to break down the data into meaningful segments without reducing them. The researchers repeatedly went through the entire material and looked at the codes to search for similarities among them, then developed broad themes that kept the data's context. These themes varied from one another in terms of scope.

Table1: Process of data analysis

Stages of Data Analysis	**Descriptions of data analysis**
Familiarising oneself with data	Transcribing data, familiarizing oneself with data and noting initial ideas
Formulation of initial codes	Arranging features of the data in a systemized approach across the data set, ordering data into their relevant codes
Identification of themes	Organizing themes from initial codes
Reviewing themes	Cross-checking themes with original codes and data, generating a thematic map of results
Defining and naming themes	Refining specifies of the themes, create clear names and definitions for each theme, finalize thematic map of findings
Writing report	The final opportunity for analysis, selection of compelling extracts of themes, relating to the research questions and reporting analysis

4. 6. Ethical clearance and considerations

Ethical clearance was obtained from the Scientific and Ethics Review Committee of the Centre for Innovative Drug Development and Therapeutic Trials for Africa (CDT-Africa),

College of Health Sciences, Addis Ababa University. Letters of ethical clearance as well as a letter of support were submitted to the selected academic and research institutions and researchers and their consent were obtained. The researcher had taken an important ethical consideration into account in conducting the study. Interviewees were briefed on the purpose of the study without any form of deception before securing informed consent from them. The researcher also has taken care of the interviewees' responses from unnecessary disclosure in a way that is abusive to their relationship with their institution and provided accurate information by examining the collected data to build a coherent justification for descriptions. Letters of ethical clearance and support are included in the Annex (III) section.

5. RESULTS

5.1. **Demography of the participants**

Interviews were conducted at four research centers and two Colleges of Addis Ababa University. In total, 14 participants were involved in the study, including two from National Veterinary Institute (NVI), two from Addis Ababa University, College of Veterinary Medicine, two from National Animal Health Diagnostic and Investigation Center (NAHDIC), four from Armauer Hansen Research Institute (AHRI), three from Addis Ababa University, College of Health Science and one participant from Ethiopian Public Health Institute (EPHI) (Table 2).

Table2: Participants demographic information

Participant ID	Name of the institution	Highest level of education	Academic rank / Position in the institution	Service year	Publication as the first Author
CDP001	AHARI	PhD	research directorate	15 year	18
CDP002	AAU, CVM	PhD	Professor	25 year	50
CDP003	EPHI	MSc	research directorate	10 year	16
CDP004	NVI	PhD	drug formulation director directorate	18 years	8
CDP005	NAHDIC	MSc	senior researcher	13 years	6
CDP006	AAU, CHS	PhD	professor	30 years	60
CDP007	AHARI	MSc	Physician	8 years	4
CDP008	AHARI	MSc	Principal Investigator	18 years	15
CDP009	AHARI	PhD	head of the one health	15 years	20
CDP010	NVI	PhD	senior researcher	13 years	7
CDP011	AAU, CVM	PhD	Associate Professor	18 years	20
CDP012	AAU, CHS	PhD	Associate Professor /east Africa one health initiative director	21 year	56
CDP013	AAU,CHS	PhD	Associate Professor	10 year	39
CDP014	NAHDIC	MSc	senior researcher	9 years	4

5.2.Study themes

During the interview sessions, participants reflected upon several concepts around zoonotic diseases, clinical trials, one health approach, and integrative practices of the public and animal health system. Participants were also able to ground these discussions by drawing

connections to their experiences in clinical research on zoonotic diseases and how these ideas may have influenced the research world. Many participants in this study reported their appreciation for the opportunity to participate in the interview as the topic is new with an appreciable idea. Some mentioned that the researchers allowed them to talk about issues that are always in their minds and planned to do more in the future. As such, five themes were identified from the data, each containing several sub-themes (Table). These themes are:-

1. Challenges in the prevention, control, and treatment of zoonotic diseases
2. One health approach to mitigate zoonotic diseases
3. Personal and institutional experiences in conducting clinical trials on zoonotic diseases.
4. Barriers in conducting clinical trials towards zoonotic diseases.
5. Strategies that promote conducting clinical trials towards zoonotic diseases.

Table 3: List of the themes and sub-themes (codes) that resulted from the data analysis

Themes	Sub-themes/Categories/codes
Theme 1: Challenges in the prevention, control, and treatment of zoonotic diseases	1.1. Lack of integration between public and veterinary health professionals and sectors, 1.2. Human capacity (lack of skilled personnel, lack of awareness and motivation) 1.3. Inadequate financial and other resources support (lack of funding, inadequate laboratory equipment, lack of infrastructure) 1.4. Limited research, experience (Lack of research materials/facilities, lack of conducive research atmosphere) 1.5. Problems related to awareness and attitude.
Theme 2: One Health approach to mitigate zoonotic diseases	2.1. Implementation of one health 2.2. Silo effect 2.3. Importance of clinical trial and other basic or applied researches intended for zoonotic diseases
Theme 3: Individual and institutional experiences in conducting clinical trials on zoonotic diseases	3.1. Personal experiences 3.2. Institutional experiences
Theme 4: Barriers in conducting clinical trials towards zoonotic diseases	4.1. Ethical and regulatory systems (delay of approval decision, complex and strict ethical and regulatory system) 4.2. Human resources (lack of skilled personnel, lack of awareness and motivation) 4.3. Administrative support, (unsupportive administrative system) 4.4. Budget and infrastructure (lack of funding, inadequate laboratory equipment, lack of infrastructure) 4.5. Lack of time
Theme 5: Strategies that promote conducting clinical trials on zoonotic diseases	5.1. Capacity building 5.2. Developing clinical trial industries 5.3. Promoting other applied researches

5.2.1. Theme 1: Challenges in the prevention, control, and treatment of zoonotic diseases

The challenges in the prevention, control, and treatment of zoonotic diseases are mentioned in many of the interviews. This theme and its five subthemes and some codes captured participants' perceptions and experiences on the challenges in the prevention, control, and treatment of zoonotic diseases. The codes (subthemes) supported by descriptions and quotes are as follows:

5.2.1.1. Lack of integration between human and animal health professionals and sectors

All participants perceived a lack of integration between human and animal health professionals as the main challenge. They mentioned that people who were engaged in the public health profession did not emphasize zoonotic diseases; they did not have the interest to get involved in research concerning zoonotic diseases. They considered dealing with the zoonotic related issue was the responsibility of animal health professionals. Moreover, participants stated that researchers who were professionals in veterinary health and those experts in public health were not collaborating to do research together. Even geographically public health institutes and veterinary health institutes were not in the same area.

"*Researchers who are working in the field of veterinary health and those who are working in human health are not working collaboratively. That is the most difficult challenge…for example, if you take Addis Ababa University, College of Veterinary Medicine, it is in Bishoftu but the College of Health Sciences in Tikur Anbesa….even geography can be also a problem to work together"(CDP013)***.**

"…I mean … people who are engaged in public health, they don't have Knowledge of zoonotic diseases… You know they consider this responsibility is for veterinarians…. They don't give much attention to zoonotic diseases ….. That is a major challenge" (CDP010).

5.2.1.2. Lack of trained manpower and inadequate finance

On the other hand, lack of human capacity, limited resources, and other related tools were reported by the majority of participants as challenges in the prevention, control, and treatment

of zoonotic diseases. They mentioned that lack of skilled manpower who specialized in the area of zoonotic diseases with knowledge of different aspects of those diseases required to propose, initiate, and conduct of any research intended for zoonotic diseases. Financial scarcity also another challenge in Ethiopia as it is also in most low-income countries; research is considered to be a luxury because of economic constraints. Participants indicated that as long as we do not have experts in the area who can deal with zoonotic diseases and well-organized financial systems, it could be difficult to prevent and control zoonotic diseases.

"....I think yes… there are several challenges, in terms of human capacity who are specialized in the field and in terms of resource both financial and another resource…"(CDP012)

"…Because we don't have tools to deal with the infection, to produce drugs such as vaccines, and so on…Even the diagnosis is very difficult for most of these diseases…they need a special laboratory for example diseases that needs complicated diagnostic techniques like brucellosis, anthrax... They need level 3 laboratories, but we do not have these …" (CDP007)

5.2.1.3. Limited research

Others described that there is a lack of baseline data due to limited research in the area and could lead to the irrational use of drugs and the scarcity of vaccines to prevent those diseases. Several neglected zoonotic diseases are not yet researched in Ethiopia.

"……The major challenges are related to issues of limited research in the area of zoonotic diseases and the knowledge and awareness of the community …" (CDP004).

5.2.1.4. Lack of awareness and attitude

Besides, lack of knowledge, attitude, and awareness in the society aggravate disease transmission between animals and humans as Ethiopia, a country that has the biggest herd of livestock in Africa where its economy largely depended on agriculture and most of the society lives closer to its animals. People don't know about those diseases and are not aware of how they get diseases from animals.

"....We have the biggest herd of livestock in Africa and people are living very close to livestock especially in the rural areas; in the whole pastoral area, there is a close link

between animals and people and increased human and animal contact leads to a risk of a high prevalence of zoonotic diseases in the area … I think this happens due to lack of awareness and scarcity of information in Ethiopia on this topic….."(CDP011)

5.2.2. Theme 2: One health and research approach intended for zoonotic diseases

This theme reflects the researchers' perceptions and experiences in connection with one health approach and different issues related to clinical trials and other basic or applied researches towards zoonotic diseases. It is divided into three further subthemes: implementation of one health, silo effect and importance of clinical trial and other applied researches intended for zoonotic diseases.

5.2.2.1. Implementation of one health

All fourteen participants considered that the implementation of one health in Ethiopia would be a beneficial approach in reducing the burden of zoonotic diseases. They considered that one health would enable earlier detection of zoonotic diseases, and therefore earlier reporting and opportunities for prevention or management of zoonotic transmission from animals to humans. They were asked about their perceptions concerning one health approach and whether they had participated in any project**,** workshop, conference, and other duties associated with one health initiative. Data suggest that some of them were involved in one health initiative activities and observed challenges and opportunities to implement it. As it is a new concept in Ethiopia, the progress of implementation so far is somehow appreciable, as different ministries are preparing a platform that helps them work together. Other participants also discussed that although some institutions started participating in one health initiative; still there is no proper health implementation in Ethiopia. The participants' further stated that where we have several emerging and re-emerging pathogens, working in isolation on the veterinary pathogen or human pathogens will not lead us any further in the control of zoonotic diseases.

"…To my knowledge, there is no proper health implementation in Ethiopia. We have a project in the Somali region. We are starting to implement one health initiative, but there is no result to show yet….. In my experience I am seeing that we still are not considering the whole ecosystem and the wildlife as part of the one health approach We started implementing one health but we have not yet exploited the full potential ….The research institute at which I am working, i.e. AHRI, is also involved in one health initiative and it has

one health unit that focuses on addressing zoonotic diseases particularly related to bovine tuberculosis and other diseases of interest like Pasteurella, brucellosis and other bacterial diseases" (CDP003).

".....in the case of one health approach,... it is a good idea to improve the diagnosis as well as the controlling and preventing method of transmission from animal to human and vice versa and there is a start of one health approach in Ethiopia in which we are just participating with other institutes working on this..... Our institution (NAHDIC) as one member is participating in prioritizing zoonotic diseases using one health approach...." (CDP002).

5.2.2.2. Silo Effect

Participants discussed the issue that there were challenges in implementing one health approach. The majority of them mentioned the existence of the silo effect in the implementation of one health and have similar challenges to collaboratively prevent and control zoonotic diseases. Silo Effect in one health refers to lack of information flowing between institutions or parts of an organization and limits the interactions between members of different sectors, thus leading to reduced productivity and capacity of collaborative working.

"....the Silo effect is the first and the most important challenge in the implementation of one health....you know there is no ministry or no office that works on one health .....Since it doesn't belong to one ministry people have their circle and work on that circle and there is a very bad history of working together....as I said the challenges that are faced on issues around working on zoonotic disease are also faced encountered in one health program. ....." (CDP012).

5.2.2.3. Importance of clinical trial and other basic or applied researches intended for zoonotic diseases

The significance of conducting clinical trials over other basic or applied researches was reported by most of the participants. In this regard, they mentioned that clinical trials had a broad concept. They stated that it was not only developing a new treatment but rather it included so many aspects it *is beyond that; a clinical trial is about. vaccine, clinical trial is about diagnostics, a clinical trial is about lifestyle.* They further mentioned that as there was evidence of a gap in the control and prevention of zoonotic diseases in Ethiopia and thus a

need for a new intervention in terms of developing new diagnostic tools, vaccines, or treatment.

"….Yes,… because the evidence is always good …I mean my work was involving both clinical trial and leadership of one health partnership. First, we should start by defining and understanding what a clinical trial is. In this perspective, someone is considering clinical trial in the context of developing a new drug but a clinical trial is beyond that; a clinical trial is about. vaccine, clinical trial is about diagnostics, a clinical trial is about any intervention .if we think of for example a trial on vaccine efficacy and safety in this country for several diseases like rabies, do we work on and invest in zoonotic diseases vaccine development, diagnostic development…yes... Clearly… yes … As I said earlier, these are diseases that are highly affecting developing countries Like Ethiopia. The problem is ours and the solution should come from us. …For example, brucellosis is one of the vaccine-preventable diseases. Anthrax is one that is vaccine-preventable. Rabies is one of the vaccine-preventable diseases. So to answer your question, do we need a clinical trial for those diseases in Ethiopia.…" (CDP012).

"….Yes, a clinical trial is more important than other basic or applied researches because you do have better, tangible information because a clinical trial is you know it is a method to evaluate the certain drug, or biological things, any kind of intervention have to first evaluate Before putting the ground….. (CDP005)

In contrast, some participants reported that as the magnitude of most of the zoonotic diseases was not well researched in Ethiopia, where there are inadequate epidemiological and other types of data, conducting clinical trial was not applicable. They thus further suggested that emphasis first be given to other basic or applied studies rather than to clinical trials.

".....For some diseases that we just, don't know enough, basic epidemiological studies would be more important to get a proper idea of what is going on. it may not be the right time to do clinical trials for these diseases because to me we are very far away from knowing the magnitude of these diseases like the rift valley or rabies. but I don't think we know what the magnitude of those diseases is. The first thing is we need to do more work in integration beyond just simply talking about one health. We need to go the grass-root level and get more involved in basic researches…" (CDP009).

"… Conducting clinical trials is good. I am not against that but I don't give priority to a clinical trial on the zoonotic disease rather the basic researches. If you do basic researches on zoonotic diseases we can generate evidence. We can do awareness creation works on zoonotic diseases and...I prefer the basic and epidemiological researches on zoonotic diseases than clinical ….Probably it might be because I don't know the magnitude of the problem but before doing a clinical trial, it is good to have adequate information on the burden of the diseases…For instance, understanding the basic characteristics of a pathogen at ultrastructure "(CDP008).

5.2.3. Theme 3: Personal and individual experiences in conducting clinical trials on zoonotic diseases

Under this theme, participants discussed different issues related their experiences in connection with clinical trials towards zoonotic diseases as well as institutional level perceptions and experiences.

Concerning personal and institutional experiences, participants claimed that there was limited experience in conducting clinical trials in Ethiopia in general. The majority of the participants stated that they had never participated in any clinical trial towards zoonotic diseases due to some country-level challenges such as institutional administrative problems and lack of funding opportunities.

"…I have no experience in conducting clinical trials for zoonotic diseases.... probably one reason is as I said we still do not have much knowledge on the epidemiology of those diseases. The second thing is a matter of prioritization of government and international bodies…As an institution, yes; I would say it is very low, to be frank. AHRI is more, I can say, working on clinical trial but when you come to specifically zoonotic diseases, it is very low. Like I said, usually, sponsors are interested in other diseases like HIV, TB, and Malaria than zoonotic diseases …" (CDP010).

On the other hand, few participants reported that they had the experience of conducting clinical trial towards zoonotic diseases involving tuberculosis, leishmaniasis which included vaccine trial, diagnostic trial, and an on-going treatment trial.

"……ya so, this is the issue so, for example, I did with leishmaniasis And you know that leishmaniasis is a zoonotic disease and therefore we have been conducting a clinical trial. I was involved in at least 7 or 8 clinical trials. Some are completed and some on-going…..so

we have new formulation and resumption to the existing treatment are to evaluated we had to come up with the short duration of treatment this has been done and even the guideline. The treatment guideline has been changed as a result of that and there has been also a negative result. Because I said close to 8 clinical trials I was engaged at least one study which was interrupted because the result was discouraging … not always to be successful and but most of the time we were successful the same thing. It was a treatment trial and evaluation of diagnostic tests … a couple of diagnostic tests evaluated now the tests are in use in the health system. The result was published and has been translated and public health use in diagnostic and treatment now. in the movement, we have one clinical trial which is vaccines for leishmaniasis, but that is on-going…"(CDP006).

5.2.4. Theme 4: Barriers in conducting clinical trials towards zoonotic diseases

Participants outlined the different barriers they faced or perceived during their research life. Most of the barriers they mentioned were similar to the challenges faced in the prevention and control of zoonotic diseases except for a few of them. The identified ones were barriers related to the handling of ethical and regulatory systems, lack of human capacity, administrative problems, financial scarcity, and other resources for conducting clinical trials. Barriers may differ generally depending on the setting in which the clinical trials are conducted.

5.2.4.1. Barriers related to ethical and regulatory systems

The majority of participants indicated difficulties with ethical and regulatory requirements, either at a national or institutional level as the main barrier. Respondents planned to conduct clinical trial experience reported experiencing regulatory problems related to approval of proposals; it takes a long time to get approval for the proposed project and that discouraged most researchers to think of and conducting clinical trials on zoonotic diseases.

"… Ya…the main challenges for conducting a clinical trial is ethical clearance and regulatory approval especially in our country Regulators and the ethical clearance are most of the time delay and make the research lose interest…" (CDP005).

5.2.4.2. Financial constraints and other resources

Most respondents report that clinical trial by itself is complicated. It is costly; it needs a long duration of time and organized documentation. They indicated that in the context of our country, as a developing country, most of the research institutions focus on basic or applied

researches which is not financially expensive. Participants highlighted barriers related to infrastructure like lack of standard laboratory to conduct clinical trials was the most frequently cited resource limitation. They indicated that zoonotic diseases posed risk to people and the environment and thus a need for good laboratory facilities, which is not available in the country. The quote from one participant could be taken as evidence that a good laboratory facility is very crucial to conduct the different phases of a clinical trial for zoonotic diseases. Lack of skilled manpower was also the most frequently cited barrier to conduct clinical trials towards zoonotic diseases.

"… it is costly, it takes time, it's complicated ….. and it needs a lot of good practice and good laboratory practice and documentation and ethical clearance also the problem …. you don't get timely feedback, or approvals from ethics committees and that takes time so the protocol would take up to 2 years to get it approval" (CDP006).

".....the human and financial capacities are the main challenges, for example, 5 years ago I was engaging in a project with the main target of building capacity in all East Africa to conduct clinical trial so. Ethiopia was a member and the other country, Kenya, Tanzania, and Uganda. the idea was to build capacity then AHARI was identified as sister institutions that probably to upgrade to be a site where we conduct a clinical trial. So we bought very few basic equipments like freezers, incubators, so on but after a couple of years everything was stopped because of a lack of capacity to run the project… so at this time, we can't even host phase two and other phases of clinical trial… probably we can do just phase one small clinical trial because of lack of capacity to do further phases of a clinical trial" (CDP008)

5.2.4.3. Barrier related to administrative issue

Participants stated that lack of support and encouragement from an institution is also another barrier. They reported failure to acquire grants as most of the grants for clinical trials were too competitive. Institutional grants were always keen to basic or applied researches and that resulted in lack of motivation from research coordinators and administrative body. Certain quotations below show these and related opinions:

"...support and encouragement from an institution is the main challenge because institutions give apriority for other epidemiological research rather than clinical trial … For example. I have submitted a protocol for the university thematic research grant in the genetics and

*behavior related topic…which was…the effect of genetics on behavior so, we want to do a clinical trial on twins, but finally it got rejected because it's a kind of a clinical trial, basic research people assume that it is a kind of luxury so, getting institutional support was a big challenge" (CDP0*13).

The other problem is administrative support especially from the institutions is limited ….in clinical trial organizational support is crucial… there is reporting for example within 24 hours you know taking immediate action it might have emergencies … It needs support from the administrative but that is not available and also There is the issue of import of goods and supplies, medication and so on" (CDP006).

5.2.5. Theme 4: Strategies that promote conducting clinical trials towards zoonotic diseases

Different suggestions were made by respondents on how to improve the conduct of clinical trials towards zoonotic diseases. Most of the suggestions were related to the challenges that have been identified above. Below are some of the common responses:

5.2.5.1. Capacity building

The most common promoting factors identified by the study participants included capacity building including change of education system since Ethiopian scientists are not that much aware of and want to do clinical trials. There must be some reform in the educational system to address the need for clinical trials. Higher learning institutions could incorporate modules on clinical trials within their teaching programs for health professionals. The other factor mentioned by participants was related to capacity building of researchers by creating a platform to bring all different researchers together to conduct clinical trial, which according to them, needs a lot of support to move forward, including from that of funding organizations, and policy and decision-makers. Participants from Addis Ababa University, College of Veterinary Medicine and College of Health sciences mentioned that the following:

"…ya…. So what could be done and I think, to begin with, education Not many scientists in Ethiopia are aware and wanting to do clinical trials, there must be some platform whereby …you know to address the need of clinical trial not only zoonotic diseases but also other diseases. I know there is some initiative in CDT Africa….to promote there is an approach to doing it as educational system .the higher learning institutions could incorporate modules about clinical trial within their teaching program and as far as I know, there is none as the

movement so, you know health professionals in general before they graduated they should get a module of a clinical trial in the final year then they will get something about clinical research …they will get something about ethics and other related issues of clinical trial …..so that is a missing link and the ministry of education and higher education if they can address it which means we will have everyone comes out of school will have an idea of what clinical trial and some might decide to do clinical trials and so have it as a career and I think with that you know the scenario might change for the future, for example, *EPHI they have a unit for zoonotic disease and also … Aklilulema institute of pathobiology ….those institutions should be leading this exercise otherwise it becomes an issue for just an interested individual, but there must be an institutional commitment they have to incorporate clinical trials in their programs and this message has to be conveyed to those institute"(CDP006).*

"ya…one thing we have to improve the capacity of researchers and funding organization they have to make open their doors for such kind of and also policymakers, Decision makers they have to be open to using outputs of clinical trials that conducted. There should be a kind of change of perception about what clinical trial is. the other one, there should be a kind of platform to bring all different professionals to work together in conducting clinical trials for these diseases unless We work together. Clinical trial for zoonotic diseases may not be successful as need."(CDP011).

5.2.5.2. Developing clinical trial industries

Other respondents talked about promoting factors in terms of infrastructure and locally developed clinical trial industry to motivate researchers to do clinical trials. The respondents reported that external partners only supported the conduct of a trial that focused on diseases of their interest but not zoonotic diseases that were relevant to the country. The respondents further stressed on the importance of locally developed tools to be self-sufficient in everything.

".. I think the first thing is they have to need to do more on capacity building in human and also the infrastructure that is initial thing otherwise I believe Ethiopia is a good site for clinical trial what we are lacking is the human capacity on the other hand. I don't see the particular challenge and particular Solution for zoonotic diseases. it's the same as any other diseases so generally in the clinical trial industry because of we don't have locally Developed tools eternal partners are influenced us ….so we have to be self-sufficient by everything, the

local scientific Community development should be We should have new tools and idea we going to do clinical trial" (CDP007).

5.2.5.3. Promoting other applied researches

On the other hand, some respondents indicated that to promote conducting clinical trials towards zoonotic diseases, there was a need to first promote epidemiological researches before thinking of conducting clinical trials because of the need to understand the magnitude and the importance of diseases in our country. So we need to have the basic information of the diseases regarding magnitude and epidemiology.

"*To promote clinical trial .i don't think. It is you know we are on the time to implement clinical trial .it should be established that we have to have to the ground otherwise it should. The country should have some industry working on pharma industry as well as biological things b/c we have to have our capacity rather than importing as a product so that if we are plan to produce or develop drugs, vaccines even we have to change our traditional medicines to market to make the marketable we have to conduct a clinical trial, so it's the time also force us to establish this think we are on the right direction, the government Addis Ababa university. Open this clinical trial-related discipline so it is nice one awarded people to participate in clinical trial". (CDP004)*

6. DISCUSSION

Zoonotic diseases are a significant public health concern that causes considerable socioeconomic problems globally (2). World Organization for Animal Health (OIE) has estimated that more than 60% of total infectious diseases, including more than 75% of emerging and re-emerging diseases in humans originate in animals (41). In this study, in-depth interviews with 14 participants provided information on researchers' perceptions and experiences in conducting clinical trials towards zoonotic diseases. Several issues around zoonotic diseases were mentioned by the participants during the interview session. Participants reported so many challenges in the prevention and control of these diseases in Ethiopia.

The main challenge for the effective implementation of zoonoses control reported by respondents was the lack of integration between human and animal health professionals, Sectors working on public health, veterinary health, agriculture, and the environment must be aware of the importance to get involved in cooperative efforts in the control zoonotic diseases. This finding is supported by many studies around the globe, which state the challenges of preventing and control of zoonotic diseases greatly due to lack of cooperation between medical and veterinary sectors in the diagnosis of zoonoses, exchange of information, organization of shared surveillance systems, common training of staff and creation of community awareness (46,47,48,49, 50). Another study reported that intersectoral cooperation is fundamental for controlling zoonoses. However, processes involved in the planning and implementation of intersectoral actions are complex (39). Additional challenges mentioned by the respondents were lack of infrastructure and other resources, such as good laboratory facilities. Participants stated that zoonotic diseases needed at most care while conducting research because they pose a high risky for humans as well as the environment.

The respondents stressed that there was a lack of good laboratory facilities such as level three and above. This result is in line with studies reported elsewhere in different African countries, which stated developing countries have a higher incidence and prevalence of zoonoses attributed to the lack of adequate control mechanisms, inadequate infrastructure (5, 7). Participant emphasized the significance of one health approach, an interdisciplinary approach to zoonotic diseases, which encourages structured collaboration and coordination between human and animal health sectors which have also been supported and highlighted in many

other studies. For example, Johnson and Hansen (51) described the proper implementation of one health that would be beneficial for the integration of public and veterinary professionals and sectors. A successful one health approach requires representation from both animal and human health sectors to identify the common mission and goals for effective collaboration. This concept is noticeable in different literature (51,52 39). Furthermore, the existence of the "silo effect" between professional sectors was also evident from the findings in this study. Participants perceived that the 'silo effect' can inhibit cross-sectional collaboration and communication. This phenomenon has also been reported by several other studies (54, 55).

The importance of conducting clinical trial towards zoonotic diseases was mentioned by participants of this research, although this is not well documented in any reviewed literature, perhaps this disjuncture is particularly relevant to developing countries including Ethiopia. Moreover, participants' talked about the significance of conducting clinical trials over other basic or applied researches in conducting clinical trials towards zoonotic diseases. In this regard, they mentioned the broad concept of a clinical trial where it is not only about developing a new treatment; it rather could include so many other aspects. As there is an evidence gap in the control and prevention of zoonotic diseases in Ethiopia, we need new intervention, a new diagnostic tool, vaccine, or new treatment. The findings highlight the challenges and promoting factors of conducting clinical trials towards zoonotic diseases in an Ethiopian context.

Researchers mentioned different barriers at all levels, starting from the system level, to the institute level, to the individual level. The greatest challenges that participants faced or perceived were related to finance, and human capacity, and ethical and regulatory systems. Participants believed that funding could become a sensitive issue to conduct clinical trials on zoonotic diseases as such, mostly a problem of developing countries, like Ethiopia. Funding for clinical trials in developing country comes mostly from Western countries in which pharmaceutical companies are based In most low-income countries, research is a luxury because of economic constraints. Since funders or most pharmaceutical companies are in developed countries, they give priority to diseases of their interest, not to those that are of high relevance to developing countries. Alemayehu et al(56) reported a lack of funding as a common obstacle and noted that the majority of funding for clinical trials comes from western countries or pharmaceutical companies established in the West. Participants stated that highly qualified personnel are required to propose, initiate and conduct clinical trials.

Such human resource development requires relatively stable, well-resourced research and higher education institutes, and well-established science governance systems, which is not the case in Ethiopia because higher learning institutions and teaching hospitals in Ethiopia have poorly prepared their graduates to conduct scientific trials and clinical research.

A study conducted in India also supports this idea, which stated that though there are half a million physicians in India with 50–60 physicians per 100,000 people, fewer than 200 have been trained in Good Clinical Practice (GCP)(57). Moreover, other studies also reported the fact that numbers of qualified researchers not reaching critical mass, research infrastructure is inadequate and funding opportunities are inconsistent and limited as factors that hampered the conduct of clinical trials in developing countries (58, 59, 60). Ethical and regulatory system obstacles emerged as the second most important barrier. Prolonged ethical and regulatory review time lead to delays in implementing grants and sometimes led grants to expire before recruitment taking place. They also reported lengthy or ill-defined approval processes, significant bureaucracy, and lack of regulatory staff with expertise in reviewing.

Similar findings have been reported in several studies around the globe especially in developing countries reporting unnecessary delays in ethical approval procedures. Complex and unreasonably strict government regulatory systems could worsen the negative feedback loop between limited research capacity and small numbers of trials conducted (61,60,62,63). Limited researches in the area were also identified as likely barriers to the conduct of clinical trial for zoonotic diseases in Ethiopia. This finding agrees with that of another study that reported that developing countries have a higher incidence and prevalence of zoonoses, and this is attributed to a lack of adequate information on their significance and distribution (5,62). Strategies for strengthening the conduct of clinical trials towards zoonotic diseases in Ethiopia need to focus on identifying country-specific problems. The study identified some promoting requirements necessary for successfully conducting a clinical trial for zoonotic diseases that are relevant in the future planning of such a strategy. Most of the promoting strategies reported by participants included the establishment of a well-organized educational system and capacity building. The result of this study reinforces the need for an educational system that integrates portions of clinical trial towards zoonotic diseases to provide students and professionals with a holistic understanding of clinical trial and zoonotic diseases as well as to improve intersectoral collaboration. As most of Ethiopian scientists are interested to involve in clinical trial studies, there must be some mechanism to address such needs. The

higher learning institutions may incorporate modules about clinical trials within their teaching programs. The other promoting strategy commonly identified by participants of this study is the issue of capacity building of researchers. A similar study conducted in Pakistan reported that lack of focus on clinical trials research in the curriculum in medical schools and teaching hospitals and lack of research-based higher educational institutions have led to a dearth of skilled personnel. Individuals with specialized training or experience in clinical trials often prefer to work abroad because of the greater opportunities, resulting in brain drain in their countries (63, 64). A standard guideline and platform should be established that address conducting clinical trials towards zoonotic diseases, especially on neglected zoonotic diseases by bringing together experts from different disciplines. This finding is supported by a study (66) which stated that capacity building is a basic strategy needed to build good clinical industries.

Additionally, policymakers should be involved to support clinical trial studies on zoonotic diseases in this country. Successful promotion of conducting clinical trials towards zoonotic diseases requires government and ministerial office involvement. Studies conducted in other countries (67, 68, 69) also stated that strategies for strengthening clinical trial capacity need to focus on enhancing political commitment and ensuring collaboration among all relevant stakeholders. Raising awareness among decision-makers and policy-makers on the burden of zoonoses in humans and animals may assist in securing political commitment and financial support for conducting clinical trials towards zoonotic diseases. Partnerships need to be forged with animal and human health organizations such as OIE, FDA, relevant pharmaceutical companies, and interested non-governmental organizations such as the World Society for the Protection of Animals (WSPA). Such partnerships would be aimed at coordinating zoonosis control activities at a regional level, mobilizing resources, and supporting the conduct of a clinical trial in the control and prevention of zoonotic diseases. Moreover, participants stressed on the importance of sharing experiences from other countries that have a success story in conducting clinical trials towards zoonotic diseases as that could encourage them to get involved in such research. For example, in other countries, there are so many clinical trials conducted on zoonotic diseases, like vaccine trials for anthrax, rabies, and other zoonotic diseases (70,71,72,73,,74,75).

7. STRENGTHS AND LIMITATIONS OF THE STUDY

A benefit of using semi-structured interviews is that it sets the boundaries of the topic and the direction of the conversation compared to an unstructured approach. Moreover, the strength of this study includes its unique approach, with a country-level focus and input from prominent experts around Ethiopia who are influential in their corresponding fields including in the areas of public health, veterinary health, and one health. The insightful data provided by participants has enabled a comprehensive understanding of challenges of conducting clinical trials towards zoonotic diseases in Ethiopia could guide researchers in overcoming challenges related to conducting clinical trials towards zoonotic diseases. The limitations of the study are that it involves a small number of participants and the findings relate predominantly to these individuals. Besides, semi-structured interviews may restrict the participants to primarily cover the topic set out by the interview guide, instead of covering all of the aspects related to their experiences. Additionally, the perspective of participants included in this research is not necessarily representative of that of their peers as such these views can't be generalized to represent all the fields in which the participants experience lies. Further large scale studies involving interviews and surveys of stakeholders including representatives from a range of institutions would be beneficial.

8. CONCLUSION AND RECOMMENDATION

This qualitative research has shown that several challenges hinder conducting clinical trials towards zoonotic diseases. These challenges include ethical and regulatory system barriers, lack of collaboration across different sectors, financial scarcity, lack of human capacity, and administrative related issues. These factors may not only contribute to clinical trials, but they are also affecting other researches designed to prevent and control zoonotic diseases. This study illustrates the importance of interdisciplinary collaboration and communication in the field of zoonotic disease control. The result of this study in collaboration with relevant literature suggests that to conduct clinical trials towards zoonotic diseases in Ethiopia, research priority areas should be identified and a formal governance body should be established with representatives from the field of human and animal health to address such priorities. In consideration of participants' perspective and relevant literature, recommendations for overcoming the challenges associated with conducting of clinical trial towards zoonotic diseases are as follow:

- The higher educations and research institutions need to incorporate modules on clinical trials within their teaching and research program with particular attention given to zoonotic diseases.
- Need for developing a plan and creating platforms to engage intersectoral communication to bring all different researchers together to conduct clinical trial towards zoonotic diseases
- Conducting further research to investigate existing gaps in the current clinical trial effort and recommending strategies to fill the gaps which will hopefully assist in the strengthening of clinical trial capacity towards zoonotic diseases.
- There should be efforts, through both training and health education, to increase knowledge and awareness among the community about clinical trials as well as zoonotic diseases.
- There is a need for improved funding for institutional and research networks that strengthens clinical trial capacity, with particular attention given to expanding opportunities for zoonotic diseases.

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APPENDIX

Appendix I: Information Sheet and Consent Form

I. Information sheet

Hello _____. Thank you so much for agreeing to speak with me. I know you have a busy schedule and appreciate your willingness to participate in this project. my name is Senait Belay, I am an MSc student in a clinical trial and This study is designed to investigate researchers' perceptions and experiences on conducting clinical trials towards zoonotic diseases in Ethiopia. It will be looking in to assess the perceptions of researchers in conducting clinical trials towards zoonotic diseases, to explore the experience of researchers in conducting clinical trial studies for zoonotic disease, to assess the practice of collaborative works between animal and public health researchers using one health approach and to identify the major challenges that hinder in conducting a clinical trial on the zoonotic disease during the study period. You and your institution are selected purposively for participation in this study. The overall purpose is to come up with a possible recommendation that is expected to contribute to the effort being made to enhance conducting a clinical trial for zoonotic diseases in Ethiopia. Today I hope to glean insight into your perceptions and experience of conducting clinical trials regarding zoonotic diseases. Any information gathered from interviews will not be used for any other purpose outside this study objective. This research is for general purpose information; no body's name will be mentioned on responses. As a result of your participation, there should be no risks for you personally or for institutions. Your participation is strictly voluntary and may be discontinued at any time during the interview. You may also decline to answer any question during this interview. For ease of note-taking, getting all of your input, and not slowing down the interview, I would like to record our conversation. The recording made today will be kept confidential and in a safe place. The only people that will hear the audio recording will be me and the person who transcribes our conversation. It will be kept in a secure location and destroyed when the study is complete. If at any time you would prefer that I turn the recorder off, please let me know, and I will do so immediately.

Institution: **Addis Ababa University**

College of Health Science, CDT -Africa

Personal Information and Address: **Senait Belay**

Mobile **09-27-01-49-86**, Email: **senaitbelay223@gmail.com**.

II. Informed Consent form

I _____have read and understand the letter of invitation to take part in the research study: Investigating researchers perceptions and experiences on conducting clinical trials towards priority zoonotic diseases.

I have received adequate information regarding the nature of the study and understand what will be requested of me. I am aware of my right to withdraw at any point during the study without penalty.

I hereby consent to participate in this research study.

Participants Signature: _____

Date: _____

Researchers Signature: _____

Date: _____

Appendix II: Interview Guide

A. Demographic data

Can you give a brief introduction of yourself, including the name of your institution, your higher level of education, service year, publications, academic rank, and position in your institution?

A. Perception

1. What do you think are critical challenges in the prevention, treatment, and control of zoonotic diseases? How do you imagine one health approach in Ethiopia?
2. How do you see the importance of doing clinical trials on zoonotic diseases? Do you believe that clinical trials are more important than other basic or applied researches towards zoonotic diseases?
3. What do you think are the perceptions of other researchers about conducting clinical trials towards zoonotic disease in your institution?

B. Experience

1. Do you have the experience of conducting clinical trials on zoonotic diseases? If yes, for which disease? What type of clinical trial? What was the result?
2. How do you see the experience and practice of conducting clinical trials on zoonotic diseases in your institution as well as the country at large? And what is the experience of your institution collaboratively work with other institutions using one health approach on conducting research particularly clinical trials for zoonotic diseases?
3. What major problems do think that would hinder conducting clinical trial towards zoonotic disease?
4. What strategies are needed to promote the conduct of clinical trials on zoonotic diseases in Ethiopia?
5. Is there anything that I did not ask you that you would like to share?

Thank you so much for participating in this interview. I appreciate your time and thoughts.

Appendix III: Ethical Approval Letter

CDT AFRICA

Center for Innovative Drug Development and Therapeutic Trials for Africa
College of Health Sciences, Addis Ababa University

Date 2/12/19
Ref No. CDT/1801/19

To Dr Senait Belay Adugna

Re: **Approval of the proposal "Investigating researchers' perceptions and experiences on conducting clinical trials toward zoonotic diseases in Ethiopia"**

Dear Dr Senait,

The Scientific and Ethics Review Committee of the Center for Innovative Drug Development and Therapeutic Trials for Africa (CDT-Africa), College of Health Sciences, Addis Ababa University, has reviewed and approved the above-referenced proposal. This approval is for a period of one year, from 02 December 2019 to 01 December 2020. Progress report shall be submitted every six months. Any change to the approved proposal must be reviewed and approved by the Committee through an amendment process prior to its implementation.

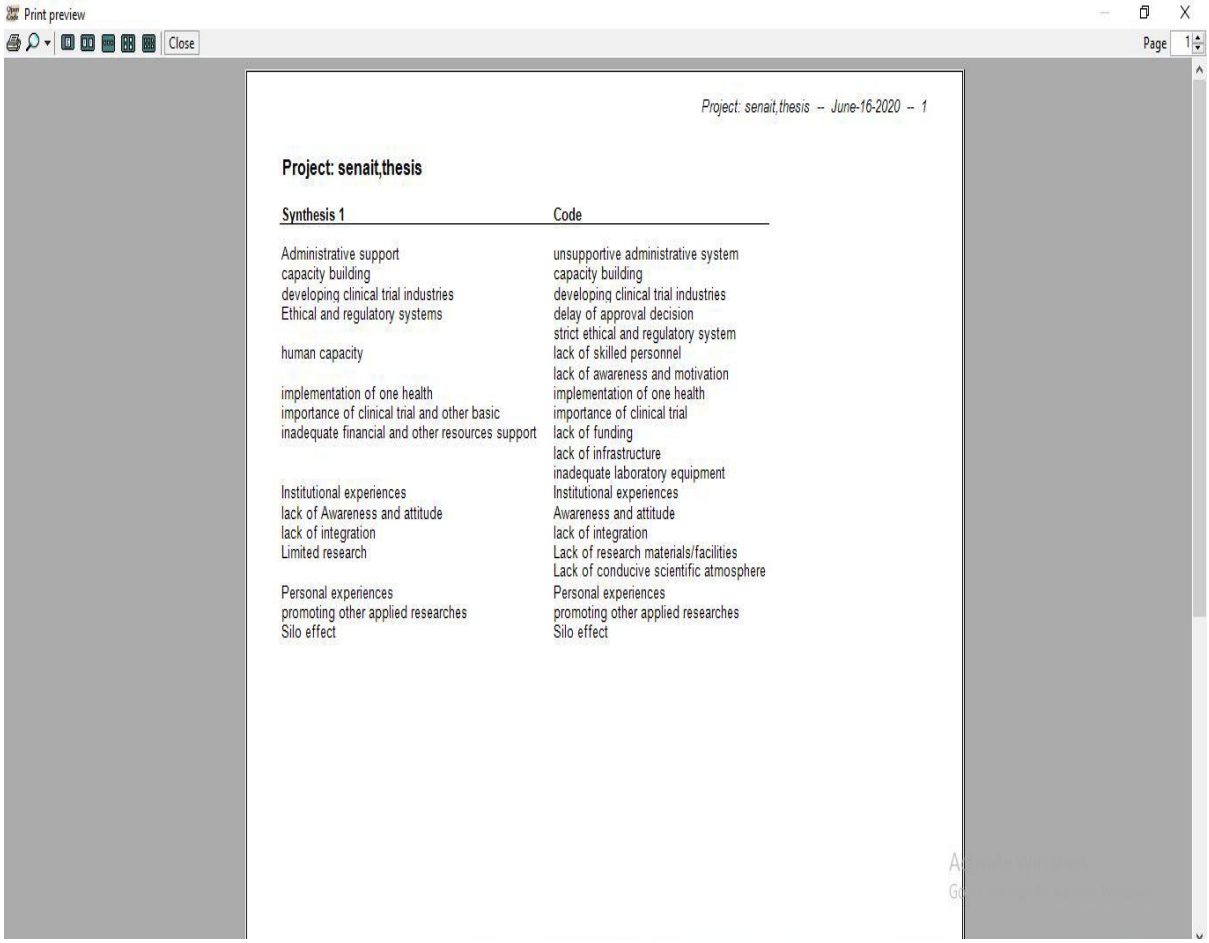
With regards,

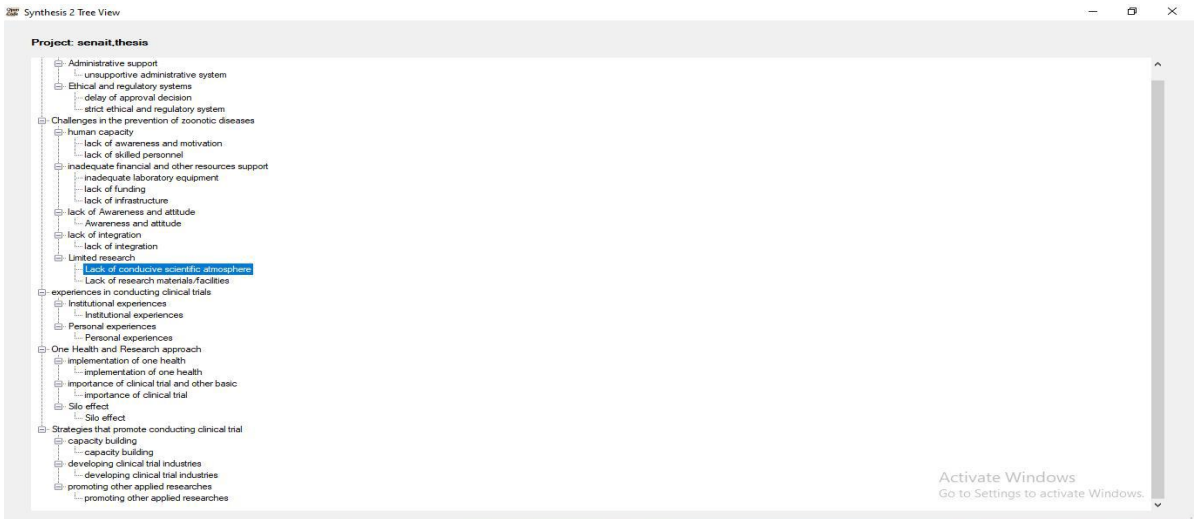
Eyasu Makonnen, PhD
Professor of Pharmacology
Chair, Scientific and Ethics Review Committee, Center for Innovative Drug Development and Therapeutic Trials for Africa (CDT-Africa)
Deputy Head, CDT-Africa
College of Health Sciences
Addis Ababa University
Addis Ababa, Ethiopia

Cc Academic Commission, CDT-Africa, CHS, AAU

A**ppendix** IV: Project synthesis **and coding process**

Synthesis 2	Synthesis 1	Code
Barriers of conducting clinical trials	Administrative support	unsupportive adm
	Ethical and regulatory systems	delay of approval
	Ethical and regulatory systems	strict ethical and r
Challenges in the prevention of zoonotic diseases	human capacity	lack of awareness
		lack of skilled per
	inadequate financial and other resources support	inadequate labora
	inadequate financial and other resources support	lack of funding
	inadequate financial and other resources support	lack of infrastruct
	lack of Awareness and attitude	Awareness and at
	lack of integration	lack of integration
	Limited research	Lack of conducive
	Limited research	Lack of research
experiences in conducting clinical trials	Institutional experiences	Institutional experi
	Personal experiences	Personal experien
One Health and Research approach	implementation of one health	implementation of
	importance of clinical trial and other basic	importance of clini
	Silo effect	Silo effect
Strategies that promote conducting clinical trial	capacity building	capacity building
	developing clinical trial industries	developing clinica
	promoting other applied researches	promoting other a


Print preview
Close
Page 1
Project: senait,thesis -- June-16-2020 -- 1
Project: senait,thesis
Synthesis 1 | Code
Administrative support | unsupportive administrative system
capacity building | capacity building
developing clinical trial industries | developing clinical trial industries
Ethical and regulatory systems | delay of approval decision
strict ethical and regulatory system
human capacity | lack of skilled personnel
lack of awareness and motivation
implementation of one health | implementation of one health
importance of clinical trial and other basic | importance of clinical trial
inadequate financial and other resources support | lack of funding
lack of infrastructure
inadequate laboratory equipment
Institutional experiences | Institutional experiences
lack of Awareness and attitude | Awareness and attitude
lack of integration | lack of integration
Limited research | Lack of research materials/facilities
Lack of conducive scientific atmosphere
Personal experiences | Personal experiences
promoting other applied researches | promoting other applied researches
Silo effect | Silo effect


Synthesis 2 Tree View
Project: senait,thesis
Administrative support
unsupportive administrative system
Ethical and regulatory systems
delay of approval decision
strict ethical and regulatory system
Challenges in the prevention of zoonotic diseases
human capacity
lack of awareness and motivation
lack of skilled personnel
inadequate financial and other resources support
inadequate laboratory equipment
lack of funding
lack of infrastructure
lack of Awareness and attitude
Awareness and attitude
lack of integration
lack of integration
Limited research
Lack of conducive scientific atmosphere
Lack of research materials/facilities
experiences in conducting clinical trials
Institutional experiences
Institutional experiences
Personal experiences
Personal experiences
One Health and Research approach
implementation of one health
implementation of one health
importance of clinical trial and other basic
importance of clinical trial
Silo effect
Silo effect
Strategies that promote conducting clinical trial
capacity building
capacity building
developing clinical trial industries
developing clinical trial industries
promoting other applied researches
promoting other applied researches
Activate Windows
Go to Settings to activate Windows.