ADDIS ABABA UNIVERSITY

COLLEGE OF HEALTH SCIENCES

CENTER FOR INNOVATIVE DRUG DEVELOPMENT AND THERAPEUTIC TRIALS FOR AFRICA

TRANSLATING ANIMAL RESEARCH INTO HUMAN TRIALS IN ETHIOPIA: CHALLENGES AND OPPORTUNITIES

BY:

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This is to certify that the thesis prepared by Askale Abrhaley entitled **Translating animal research into human trials in Ethiopia: Challenges and opportunities** and submitted in partial fulfillment of the requirement of the degree of masters of science (MSc) in Clinical trials complies with the regulation of the University and meets the accepted standards with respect to originality and quality.

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LIST OF ABBREVIATIONS

AAU	Addis Ababa University
AHRI	Armauer Hansen Research Institute
bpm	beats per minute
CDT-Africa	Center for Innovative Drug Development and Therapeutic Trials for Africa
COREQ	Consolidated Criteria for Reporting Qualitative Research
CRO	Contract Research Organization
DSMB	Data and Safety Monitoring Board
EPHI	Ethiopian Public Health Institute
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HIV/AIDS	Human Immunodeficiency Virus/Acquired Immune Deficiency Syndrome
IND	Investigational New Drug
IRB	Institutional Review Board
NAHDIC	National Animal Health Diagnostic and Investigation Center
NVI	National Veterinary Institute
PI	Principal Investigator
UK	United Kingdom
USA	United States of America

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ABSTRACT

Background and Objectives: Although the goal of translational research is to bring biomedical knowledge from the laboratory to clinical trial and therapeutic products for improving health, this goal has not been well achieved as often as desired because of many barriers documented in different countries. Therefore, the aim of this study was to investigate the challenges and opportunities of translating animal research into human trials in Ethiopia.

Methods: A descriptive qualitative study, using in-depth interviews, was conducted in which preclinical and clinical trial researchers who have been involved in animal research or clinical trials as principal investigator were involved. Data were analyzed using thematic process.

Results: Six themes were emerged for challenges: lack of financial and human capacity, inadequate infrastructure, operational obstacles and poor research governance, lack of collaboration, lack of reproducibility of results and prolonged ethical and regulatory approval processes. Furthermore, four themes were synthesized for opportunities: growing infrastructure and resources, improved human capacity and better administrative processes, initiatives for collaboration, and similarities between species.

Conclusion and recommendations: The study found that the identified characteristics/features are of high importance either to hurdle or enable the practice of translating animal research into human trials. The study suggests that there should be adequate infrastructure and finance, human capacity building, good research governance, improved ethical and regulatory approval process, multidisciplinary collaboration, and incentives and recognition for researchers to overcome the identified challenges and allow translating of animal research into human trials to proceed more efficiently.

Keywords: *Animal research, Challenges, Ethiopia, Human trials, Opportunities, Translational research*

1. INTRODUCTION

1.1. Background

Animal models have been an invaluable tool for inferring human biological responses from basic biology to translational medicine and clinical trials (Rhrissorrakrai *et al*., 2015). This is because most scientists agree that experiments involving the use of animals have great potential like facilitating innovation, developing platform technologies and very often providing a link with clinical trials. In addition, animal experimentation is useful in exploring disease mechanisms, validating and testing new targets for drug research and providing insights into drug toxicity and interactions (Kehinde, 2013).

Although improving health is the common objective of basic life science and biomedical research, this goal has not been well achieved as often as desired or needed. One well-designed study found that less than 25% of highly promising biomedical discoveries resulted in a published randomized clinical trial and less than 10% were established in clinical practice within the last 20 years (Contopoulos-Ioannidis *et al.,* 2003). There are two broad pathways to improve human health. The first is through public health initiatives designed and enacted on the basis of behavioral research through the application of current knowledge, public education, and policy change. In the second pathway to improve human health, scientific discoveries must be translated into practical applications, and such discoveries typically begin at the bench with basic research in which scientists study the disease at a molecular or cellular level for its progress to the clinical level, and/or its delivery to the patient's bedside. Translational medicine focuses on the improvement of human health by bridging the gap between basic science research and clinical practice (Albani and Prakken, 2009, Woolf, 2008). This bridging is done at two distinct levels: at the level of basic science research in the laboratory and in preclinical studies, translating it into new devices or treatments (‘from the bench to the bedside’); and at the level of clinical practice, transferring the new treatments into the daily routine (Jiang *et al*.,
2013, Machado *et al.,* 2015).

Much clinical research follows from animal research (Pound and Bracken, 2014). The practice of using animal models of human diseases for drug testing is common practice among biomedical researchers and scientists (Singh *et al.,* 2016). Recent attempts to improve translation within the animal research community include the “co-clinical trial” in which preclinical trials explicitly

parallel ongoing human phase I and II trials (Chen *et al.*, 2012) and the development of a scoring system to identify biomarkers that better predict therapeutic success (Wendler and Wehling, 2012). Translational research has become an issue of increasing importance to scientists and governments around the world (Jiang *et al.*, 2013). It has been estimated that 60–80% of animal experimentation used for pharmaceutical research and development are in the characterization of promising candidate drugs and about 5–15% are used in the discovery and selection process (Singh *et al.*, 2016). Of the one-third that enter into cancer clinical trials, as little as 8% of drugs pass Phase I successfully (Mak *et al.*, 2014). The majority of drug trials investigated in Ethiopia are on the use of already approved drugs to optimize treatment (Vischer *et al.*, 2017). The animal studies for those clinical trials are conducted in other countries. In Ethiopia, there are many in vivo/preclinical studies conducted particularly on herbal medicines. However, none of them translated to human trials.

1.2. Statement of the Problem

The academy of medical sciences in UK (2010) reported that in the USA, UK and several other countries, the substantial investment in animal based biomedical research has led to considerable success in terms of scientific discoveries, but is regarded as failing to achieve comparable advances in diagnosis, prevention and treatments with implications for both the health of populations and the productivity of national economies. This apparent gap between discovery and its transformation into commercial outputs has been explained in terms of the poor predictiveness of animal models and a lack of scientific rigor that results in a lack of beneficial effect in subsequent clinical trials (Contopoulos-Ioannidis *et al.*, 2003, Unger, 2007). The other blocks are regarded as arising firstly, through the difficulties and time lags that often occur in the translation of laboratory-based research into new methods for diagnosis, therapy and prevention and their first testing in humans (Type 1 translation); and secondly, through time lags in the translation of results from clinical studies to their adoption in everyday practice (Type 2 translation) (Sung *et al.*, 2003).

The complete translation continuum is a complex process and takes an average of 17 years for research evidence to reach clinical practice (Westfall *et al.*, 2007). Regardless of the time and complexity of translating findings into care, there is a continued need to promote the concept of translational medicine among clinicians, basic science researchers, biotechnologists, politicians, ethicists, sociologists, and investors to further improve efficiency of these translational processes (Littman *et al.*, 2007). Conversely, there are barriers, which hinder the translation of animal research

to clinical medicine documented in different countries. These barriers include: a lack of a 'culture of translation' within institutions (Snape *et al.*, 2008), inadequate infrastructure, including a lack of facilities to conduct clinical research (Fudge *et al.*, 2016); and an inadequately trained workforce and difficulties retaining those who do possess the necessary skills (Restifo and Phelan, 2011). Even though collaboration is proposed as a key requirement for translational research, it is inhibited by the compartmentalization of departments within universities and hospitals, a cultural divide between scientists and clinicians, and a university system that rewards individual achievement rather than team work practices (Snape *et al.*, 2008, Restifo and Phelan, 2011). In Ethiopia, several important barriers including low stewardship and governance capacity, limited funding allocation, weak regulatory and administrative systems, few learning opportunities, limited human and material capacity, poor incentive for conducting research, lack of local investigator initiated clinical trials, and lack of awareness, confidence and motivation to undertake trials (Franzen *et al*., 2013, Franzen *et al*., 2017) which limited the capacity to undergo clinical trials are recognized (Deressa *et al.*, 2018). However, less is known about the challenges and opportunities of translating animal research into human trials in Ethiopia from the perspective of those largely held responsible for conducting translational research: basic and clinician scientists. Therefore, the aim of this study was to investigate the challenges, which hinder translation of animal research into human trials in Ethiopia, and to identify possible opportunities.

1.3. Significance of the Study

Since, translational research is the transfer of knowledge gained from basic research including animal research to new and improved vaccines, devices and treatments to improve human health, identifying the challenges and opportunities of translating animal research into human trials is very essential to make the process efficient. By identifying the major challenges and opportunities of translating animal research into human trials in Ethiopia, the study is expected to help in informing policy-makers and implementing specific and efficient institutional and other relevant planning options towards developing enhanced translational research practice in both research and academic institutions that would benefit community health. It is also hoped that the study will give a good understanding and an insight about translational research for other researchers and policy-makers so that they engage more in this issue in the future.

2. LITERATURE REVIEW

2.1. Translational Research

Translational research is generally regarded as a "bench to bedside" discipline designed to direct the findings of basic research to the production of new medications (LoRusso, 2009). Translational research may also be viewed as important in fulfilling the desire of basic scientists to have their work used for the benefit of mankind (Wehling, 2008) and to ultimately reverse the decline in drug discovery and productivity. Translational research has been further envisaged (i) as a process for ensuring the bidirectional flow of information from the research laboratory to the clinic and vice versa (Sung *et al.,* 2003) and (ii) as encompassing all elements of the drug development process from the initial screening for chemical leads to target identification to clinical proof of concept (FitzGerald, 2005).

Across different fields, there are a variety of models that depict the phases of the translational research process, ranging from two to five stages (Westfall *et al.*, 2007, Rubio *et al.*, 2010). For example, the National Institutes of Health (NIH) and the Institute of Medicine's Clinical Research Round table describe translational research in two defined stages, defining T1 as "the transfer of new understandings of disease mechanisms gained in the laboratory or preclinical studies into the development of new methods for diagnosis, therapy, and prevention and their first testing in humans, and is generically considered as representing the translational component and T2 described as "the translation of results from clinical studies into everyday clinical practice and health decision making" (Zoellner and Porter, 2017). Others, have described the translation spectrum in more distinct phases, including T1_T3 (Westfall et al., 2007), T1_T4 (Khoury *et al.*, 2007), and T0_T4 (Blumberg *et al.*, 2012) which include T0 (basic biomedical research), T1 (clinical translation), T2 (demonstrating efficacy), T3 (translation to practice), and T4 (translation to populations).

A key element of any translational initiative is the development of cellular, tissue, and animal assays that can reliably predict human responses and facilitate the successful advancement of new chemical entity from the "bench" to the "bedside". This is a complex process involving the transition of potent, drug like new chemical entity from cellular to animal assays and their subsequent transition to the clinic (Wehling, 2008).

2.2. Animal Research Supporting Clinical Trials

To improve human health, scientific discoveries must be translated into practical applications and such discoveries typically begin at the bench with basic research in which scientists study the disease at a molecular or cellular level for the progress to the clinical level, or the patient's bedside (Zhang, 2011). Preclinical experiments represent the original science underlying the development and implementation of novel clinical trials and are mostly always necessary precursors of clinical trials (Lowenstein and Castro, 2009). They provide valuable animal pharmacokinetic and pharmacodynamics information that can be used to plan the starting dose and schedule of subsequent phase I studies. Beyond these data, prior to initiating clinical studies there should be a reasonable expectation of benefit in humans based on results of *in vivo* efficacy experiments (Goodwin *et al.*, 2012).

Laboratory animals are also often used as models for understanding of disease processes and to test new vaccines and medicines. Very often these types of research draw on findings derived from basic scientific research (Schuler, 2002). For example, animal models using the chimpanzee and monkey were employed extensively for the study of hepatitis B and poliomyelitis leading to the development of effective vaccines against these diseases (Kehinde, 2013). Similarly, much of the current knowledge about hepatitis C has been derived from studies in the chimpanzee as, for a long time; it was the only non-human host for the virus. Unluckily, unlike hepatitis B, an effective vaccine against hepatitis C is yet to be discovered. Animal models may be difficult to find or develop for some diseases such as HIV/AIDS and some cancers (Cohen, 2003). This is due to the complex pathogenesis of these diseases and their many different subtypes in humans and animals, which makes it inherently difficult to study them and develop successful animal models (Cohen, 2003, Perel *et al.*, 2007, Kehinde, 2013).

Another essential area of animals as models for human diseases involves the use of genetically modified animals. Effective treatment has been developed for some types of cancer, such as breast cancer (tamoxifen) and prostate cancer (goserelin), based in part on the study of transgenic mice that express human receptors on their cells, which were used as replacements for primates. At present, it can be argued that the use of genetically modified animals as models has allowed researchers to generate more accurate and appropriate models of human diseases that have facilitated progress and has made it more likely that research findings in such models will transfer to human subjects more

quickly. Most biomedical scientists working in the field are of the view that there are often enough similarities between mice and humans to make informative comparisons. Examples include findings from models used for diabetes, deafness, psychiatric disorders, neurodegenerative disorders and some cancers (Kehinde, 2013).

2.3. Trends in Clinical Translation of Animal Research

The term "translational research" first appeared in PubMed in 1993, but it did not attract extensive attention until around 2000 (Butler, 2008). It has been in use for over 30 years, but has really come into focus in the health field in the last ten years and is now central to international health policy, research and funding initiatives (Drolet and Lorenzi, 2011). The need for translational research is based on the evidence that much research in the life sciences has failed to improve human health, and it offers itself as a solution to tackle intractable health problems (Leonelli and Sunder Rajan, 2013).

A number of initiatives have been established at policy level with the aim of reducing perceived bottle necks in translational research in order to accelerate the translation of scientific knowledge into effective health measures with health benefits for patients and wealth benefits for the nation (Heller and de Melo-Martín, 2009, Collins, 2011).

2.4. Challenges of Clinical Translation of Animal Research

The discovery and development of drugs is an endeavor that has become increasingly more challenging (Hummel and Whiteside, 2017). Despite technologic advances in throughput, there is a perception that the drug discovery process has slowed down, resulting in a so-called "productivity crisis" in the pharmaceutical industry as a whole (Cook *et al.*, 2014).

The essential role of translational research in ensuring rapid progression of basic scientific knowledge to patient benefit has been emphasized for more than three decades (Butler, 2008). Although translational research has shown promise for understanding and treating human disease, impediments to fulfilling this potential have also been identified during this period. The main barriers identified across the areas of clinical translation are differences in culture and mindset between basic and clinical scientists, shortage of trained investigators, lack of role models and training opportunities, inadequately protected research time, poorly defined research-based career

paths, the culture of valuing clinical care over research, poor infrastructure, lack of interdisciplinary research collaborations, high research costs and lack of relevant funding streams, lack of incentives and rewards, and ethical and regulatory issues (Butler, 2008, AH. Kaji *et al.*, 2010, Homer-Vanniasinkam and Tsui, 2012).

Several studies identified complex regulatory processes, such as ethics and research governance, as barriers to translational research, in effect slowing it down (Chen, 2009, Zhang, 2011, Stephens *et al., 2013).*

Cultural differences between the two groups of investigators largely stem from the lack of communication, coordination, connection, and differences in education and training, and different goals and reward mechanisms (Butler, 2008). Moreover, lack of reproducibility of basic research findings is perhaps the major problem with preclinical testing of therapies and it likely results from numerous factors, including: failure to use standardized animal models, research protocols, terminology, and methods of analysis; lack of randomized study design; lack of blinding of investigators; and methodological errors, for example failure to control basic physiologic parameters. Furthermore, use of animal models that do not adequately approximate the clinical setting (e.g. comorbidity) and failure to disseminate negative results are some of the barriers at preclinical setting (Koontz *et al.*, 2017, Seyhan, 2019, Parrish *et al.*, 2019, Patel *et al*., 2020). Together, these issues contribute to various checkpoints between the phases of translational research including the "valley of death" that exists between preclinical research and clinical trials (Butler, 2008).

2.5. Enablers of Animal Research Translation

The depth between basic and clinical researches is sometimes labeled as the "valley of death", as this particular chasm has existed in the ecosystems of bench and bedside research for over 30 years (Butler, 2008). It is suggested that there is a need for building the bridge from bench to bedside (Adams, 2008). Other scientists believe in the need for a two-way dialogue and interaction between scientists in preclinical drug discovery and clinical developers for effective translational research in drug development (O'Connell and Roblin, 2006). A study (Chen, 2009) has argued that translational research is a project that involves multiple interactions between different actors, and states that simple linear translation models are insufficient to grasp complex scientific medical realities.

To overcome the barriers in translation of animal research to clinical trials, increased sustained funding dedicated to T1 translation is clearly essential to enable innovative approaches towards research. These are the building of research units that incorporate multidisciplinary groups which may involve bioinformaticians, statisticians, engineers, basic scientists, and clinicians; increasing expert support in regulatory issues and clinical trial design and conduct, and initiation of forums for interdisciplinary discussion. The latter encourages discussion and networking between basic scientists and clinicians, initiation of interdisciplinary collaborations and the building of appropriate research teams (Homer-Vanniasinkam and Tsui, 2012). Although intellectual property issues are important in the interaction between academia and industry, recent research shows that the public–private partnership is increasingly perceived as supremely important for the translational effort (Littman *et al.*, 2007).

3. OBJECTIVES

3.1. General Objective

- ✓ To investigate the challenges and opportunities of translating animal research into human trials in Ethiopia.

3.2. Specific Objectives

- ✓ To identify the challenges of translating animal research into human trials.
- ✓ To explore opportunities for translating animal research into human trials.

4. METHODS

4.1. Study Setting

Qualitative data was collected from a study that was conducted in different research and academic institutions in Ethiopia including Armauer Hansen Research Institute (AHRI), Ethiopian Public Health Institute (EPHI), National Animal Health Diagnostic and Investigation Center (NAHDIC), National Veterinary Institution (NVI), and Addis Ababa University (Aklilu Lemma Institute of Pathology, College of Health Sciences and College of Veterinary Medicine and Agriculture). Armauer Hansen Research Institute, Ethiopian Public Health Institute, AKlilu Lemma Institute of Pathobiology and College of Health Sciences are found in Addis Ababa, which is the capital city of Ethiopia. National Veterinary Institute and College of Veterinary Medicine and Agriculture are located in Bishoftu. The National Animal Health Diagnostic and Investigation Center is located in Sebeta. Most of animal researches and clinical trials that have been conducted so far in the country involved one or more of these institutes. All the five institutions have strongly contributed to health research in Ethiopia. AHRI is a center for clinical trial research, EPHI has been involved in preclinical studies related to animal and public health, NAHDIC and NVI are dedicated research institutions working majorly on animal health related preclinical and clinical researches and sometimes involved in public research, and Addis Ababa University (AAU) has been involved in conducting both preclinical and clinical trial research.

4.2. Study Design

A descriptive qualitative research approach was used to investigate the challenges and opportunities of translating animal research into human trials in Ethiopia from preclinical and clinical trial researchers' perspective.

4.3. Study Participant

Study participants including basic and clinical trial scientists (researchers) at the study sites were contacted and interviewed. The interviews conducted were audio recorded and transcribed verbatim. Each interview took, on average, about 45-60 minutes.

4.3.1. Inclusion criteria

Pre-clinical trial and clinical trial researchers with position of assistant professor and above from academic institution and assistant researcher and above from research institutions, and who have been involved in animal or clinical trial research as a principal investigator (PI) were included in the study.

4.3.2. Exclusion criteria

Researchers who have been involved in pre-clinical research or clinical trials as co-investigator and researchers who have never been involved in pre-clinical or clinical trials were excluded from the study.

4.4. Participant Recruitment

Intensity purposive sampling technique was applied both in the selection of study participants as well as research institutes and academic institutions to get deeper information. Participants were sampled following their willingness to participate. The sample size was determined based on information saturation.

4.5. Data Collection Instrument

A qualitative data was collected from November 2019 to April 2020. The data was collected using in-depth interview technique. For this purpose, semi- structured interview guide was designed and prepared in English with open-ended questions related to the objectives of the study that encouraged participants to describe their own understandings and opinions and allowed identification and exploration of themes and hypotheses that might not have been anticipated (see Annex-3). The guide was used with flexibility; it included general questions about challenges, and opportunities in translating animal research into clinical trials. Interview questions did not target a specific trial but rather on participant`s basic research and trial experiences in general. The focus of the interview guide was to gather information on the respondent's socio-demographic characteristics, the challenges, and opportunities of translating animal research into human trials.

Participants were informed that the interviews were part of an MSc thesis project. There was no need for a translator as the interviewer (principal investigator) speaks both Amharic and English. The interviews took place in a private room/ office of each interviewee allowing confidentiality. Summaries and observations were written down in a field diary by the interviewer immediately after each interview and audio recording. These notes and audio records were useful during data analysis. Interviews continued until information saturation was reached. Saturation of information is considered to be reached when few or no new concepts were raised (Charmaz, 2006).

4.6. Data Quality Assurance

The investigator followed rigorous criteria using several strategies to maintain the trustworthiness of the study. The semi-structured interview guide was reviewed by two academic advisors and one postdoc scientist. Routine on site interview, supervision, and checking were carried out by principal investigator. The collected written and audio-recorded data were checked for completeness, accuracy, clarity, and consistency by the principal investigator on daily basis. To check the credibility of the study, some of the study participants were invited to review the findings and ideas whether they correctly represented their point of opinions. In addition, validity of the data was checked by theory triangulation and investigator triangulation (peer-debriefing) in which experts from different and same disciplines reviewed the finding, respectively, both during and after analysis. Moreover, a rich description was used to convey the findings of the study so as to help the reader to understand it easily.

4.7. Data Management and Analysis

All interviews were transcribed verbatim and reviewed based on the transcript and original recordings. Thematic analysis was conducted using NVivo Plus version 12 qualitative data analysis software. English transcripts were analyzed in their original language. After repeated readings of the transcripts, data was grouped and sorted by question using auto coding, and coding was done by coding important features of the gathered data in a systematic manner (Annex-4). The coding frameworks were discussed amongst advisors before agreeing on a final version. The analysis was focused on challenges and opportunities in translation of animal research into human trials in the Ethiopian context. Notes (memos and codebook) were taken during the analysis to ensure that it is reflective. Similarities, differences, and patterns were identified across the interviews and sub-themes, which give structure to the over-arching themes before refining them. The data set was re-read to check for coherence of data within themes and for clear and identifiable distinctions between themes and sub-themes. Finally, revision was made on the data set to code any additional data that had been missed in previous coding stages. After discussions with advisors who are experts in various disciplines, decisions were made on final definition and naming of the themes and sub-themes.

4.8. Ethical Considerations

Ethical approval was only sought from the Scientific and Ethics Review Committee of the Center for Innovative Drug Development and Therapeutic Trials for Africa (CDT-Africa), College of Health of Sciences, Addis Ababa University. The research project did not require access to private and sensitive information or health-related data or materials. Participants of the study were asked for verbal and written consent before participating in the study (Annex-2). Information sheet about the study, why study participants were selected, and what is expected from participants were given prior to the interviews. Participants were assured of confidentiality of information in the course of the study. They were briefed on the objective and background of the research project and the right to leave the study any time. Anonymity and confidentiality was guaranteed and thus no names of participants are disclosed in the thesis. All participants were asked for their agreement to be audio recorded during the interview, which averaged 45-60 minutes per study participant. This study was conducted with adherence to consolidated criteria for reporting qualitative research (COREQ) (Tong *et al.*, 2007).

5. RESULTS

5.1. Characteristics of Study Participants

A total of 17 researchers who have been involved either in preclinical studies or clinical trial or both participated in the in-depth interviews; eight were based at research centers, and nine at a university. Two to four interviews were conducted in each institution. Saturation of information was reached after the first 14 interviews. Ten participants had been involved in pre-clinical research, three in clinical trial, and four both in preclinical and clinical trials. The participants had experience in a diverse range of medical professional domains. Participants had between 5 and 30 years of working experience in preclinical and clinical research (Table 1). One participant have been involved in translating a study conducted on animal experiments using herbal medicine against helminth into human study up to phase-2 using a tablet formulated as a drug, but the drug was found to be inferior than the standard treatment. Another participant has been involved in the preclinical part of herbal medicinal plant against liver cancer and did not proceeded to the next step as the ethics committee didn't allow him. Moreover, a participant has been involved in preclinical studies using herbal medicine and formulated as ointment and now they are waiting for ethical approval to conduct phase-1 clinical trial in collaboration with other research institution in Ethiopia.

Table 1: Characteristics of study participants

Terms	Categories		Number of participants
Area of expert	Pharmacology		5
	Clinical pharmacology		1
	Molecular microbiology		1
	Biotechnology and virology		1
	Infectious diseases		1
	Clinical pharmacy		1
	Microbiology		1
	Infectious disease epidemiology		1
	Pharmaceutical chemistry		1
	Pulmonary pediatrics and infectious diseases		1
	Epidemiology and biostatistics		1
	Zoonosis		1
	Trans-boundary diseases		1
Domain of experiences	Preclinical trials plus others		10
	Clinical trials plus others		3
	Both (preclinical and clinical trials) plus others		4
Years of research experiences	5-20 Years		12
	>20 Years		5
Role as a PI in research	Preclinical	1-6 projects	10
		20-30 projects	3
	Clinical trial	1 project	4
		5 projects	2
Focus area in terms of diseases/ Pathogens/ others	Studied in preclinical studies for both animal and human	African horse sickness, Anthrax, Anti-infertility, Ant-inflammation, Anti- pyretic, Anti-spasmodic, Asthma, Diabetic mellitus, E.coli, Fasciola hepatica, Fowl cholera, Pasteurellosis, Leishmania, Schistosomiasis, Fowl typhoid, Haemonchus contortus, Helminthes, Hypertension, Leishmania, Liver related diseases, Malaria, New castle disease, Infectious bursal disease, Histoplasma, Non-communicable neurodegenerative diseases, Phytogenics, Rabies, Relapsing fever, Rota virus, S.aureus, Salmonella, Trypanosomiasis, Tuberculosis	-
	Studied in clinical trial	Cervical cancer, Cholera, Diabetic mellitus, Helminthes, Hepatitis B, HIV, Malaria, Meningitis, Tuberculosis, Visceral leishmaniasis	-
Phase of study (Note: one person can conduct many studies at each phase)			**Number of studies**
	Phase 1		5, of them 1 waiting for approval
	Phase 2		3
	Phase 3		4,of them 1 waiting for approval
	Phase 4		1
	Not applicable (For preclinical research and vaccine trials)		11
Type of trial for clinical trial and preclinical studies	Drug		7
	Vaccine		7
	Diagnostic tools		2
	Pharmaceuticals dosage formulations on traditional medicinal plants		2
	Medicinal plants		8

5.2. Challenges and Opportunities for Translating Animal Research into Human Trials

Using thematic analysis, six major themes were identified for challenges: lack of finance and human capacity, inadequate infrastructure, operational obstacles and poor research governance, lack of collaboration, lack of reproducibility of results and prolonged ethical and regulatory approval processes. Moreover, four themes were identified as opportunities: growing infrastructure and resources, improving human capacities and better administrative processes, initiatives for collaboration and similarities between species (animal and human). Representative quotes supporting each theme are presented, along with unique identification numbers of participants in brackets. The themes were prioritized based on the number (frequency) of interviewees who mentioned each theme as a challenge or opportunity.

5.2.1. Challenges for translating animal research into human trials

Theme 1: Lack of finance and human capacity

Nine of the participants mentioned that the major constraint for translating animal research into human trials is lack of funding. It was mentioned that translating animal research findings into human trials, particularly the clinical trial part requires a huge investment. Hence, if you do not have an adequate supply of fund from industries or other interested donors it is difficult to sustain translational research. Many brilliant Masters and PhD students who went abroad for education did not return because of that reason. Some who returned to the country after completing their education but who got the second chance to go abroad for their post docs in European and American universities did not come back because they learned that the research environment in Ethiopia was not attractive. Most academicians are frustrated to conduct thematic research projects related to translational research because of financial constraint and poor budget administration as mentioned by the study participants. The interviewees also stated that the government does not allocate enough money for translating animal research into human trials and there is a very little core research fund, which is less than five hundred thousand Ethiopian birr per annum. As reported by the participant:

"It is only the building that the government has provided. All the rest that we have managed to buy, among others, including vehicles, research laboratory equipment were secured from international funders on a very competitive basis. Some who are not able to get funding from foreign funders get frustrated and they…just compete for the local small grant which is less than five hundred thousand

that can only use to cover…per diem, support MSc and PhD students work and buying simple reagents you can't even use it for fuel purchasing during field works. Unless there is core local research funding we should not expect any…real…development in the drug or diagnostic device or anything it could be used in clinical trial, we would end up in post clinical trial researches/approved drugs" (A1, clinical trial researcher*).*

On the other hand, two preclinical trial researchers stated that funding was not a problem; instead it was a financial management problem.

Besides, eight participants felt that human capacity, be it from researchers' side or the ethics experts and regulators side, was the critical factor. Respondents stated that there were poorly qualified researchers in terms of knowledge, skill, training, and experience. There is minimum awareness and preparedness, attitude problems of the research community for such type of research. Moreover, there is a poor research literacy of researchers in clinical trials and low physicians' interest to conduct research on traditional medicine. As the study participant noted:

"…There is also an attitudinal problem in researchers…most common sign of the completion of a project is this publication. So findings from a preclinical study once they are published people do not think of taking the finding to the next level" (A8, preclinical and clinical trial researcher).

Another participant noted*:*

"Physicians' interest is another challenge because they tend to the conventional medicines though traditional medicine is the mother of modern medicine as illustrated by a number of discoveries of conventional medicine which are originated from traditional medicines. So there are some blurred visions by medical doctors" (A14, pre-clinical trial researcher).

Another participant also noted that*:*

"…In my view the main challenge is lack of capacity of researchers in terms of knowledge and skill" (A4, preclinical trial researcher*).*

Problems related to regulatory and ethics committee, including the capacity of personnel in terms of knowledge, skill, and experiences to judge the advantage and disadvantage of studies is another challenge reported by the participants.

"I think it is related with…the capacity of our ethics committee in reviewing and approving studies like this [translational study] is not that much or it is limited…there is no experience so…as a country that starting…this kind of initiatives I think everybody is afraid that what if something happen and you know the level of protection you have to consider what if this study is done on myself or my family or my kids. So allowing that to happen from the ethics committee side is difficult because there is no experience and…." (A7, preclinical and clinical trial researcher).

This scientist went on to express doubt on the ethics committee in facilitating the conduct of translational study despite the fulfillment of all requirements and warned that, *''However, I would like also to say that no ethics committee would say no to translational study if you fulfill…whatever the GCP requirement…if the team are trained, knowledgeable skilled and if you show that you have the resource, infrastructure. But clinical trial, they do approve our clinical trial proved that you fulfill everything".*

Theme 2: Inadequate infrastructure

While a general lack of infrastructure and facilities were thought to hinder the translation of animal research into human trials, most participants (n=9) stated that lack of well-equipped, furnished and accredited laboratory facilities and shortage of resources like laboratory supplies and consumables were major barriers. As noted by the study participants:

"So if you want to do experiments on animal models that laboratory has to be GLP accredited but there are no accredited laboratories" (A17, preclinical and clinical trial researcher).

Another scientist noted:

"No appropriate infrastructure…most of the institutes have really rudimentary kind of research laboratory and only…to support students and institutional activities…you cannot expect for big research outcomes to bring about change on the health and development of our country…." (A1, clinical trial researcher).

"No facilities, for example, you know simply doing in vivo studies does not make your compound to be…eligible for a clinical trial. So you need to do…pharmacokinetics studies you need to…see the probable mechanism of action of a particular agent for that then you need to have cell lines because

you can easily manipulate cell lines and it is good to understand and how the agent acts in order to produce the effect so that you could see in in-vivo experiments. So you do not have such facilities and without completing these kind of studies…it is very difficult to move into a clinical study" (A8, preclinical and clinical trial researcher).

According to the interviewees (n=2), lack of organized center specialized in translational research was also perceived as a barrier. As noted by the study participant:

"…Teaching of clinical trials that will only have trained manpower in clinical trials unless you have the institution for translational research in which these people could be engaged, I do not think it will have an input, they will end up in the university teaching on clinical trials….However, it is at least a good start and that would help to convince the government…at least to allocate for this" (A1, clinical trial researcher).

Theme 3: Operational obstacles and poor research governance

Lack of commitment from the researchers, institutions and the government, poor research management, including poor financial management or inefficient use of resources and poor quality control, lengthy and complex logistics and difficult purchasing process, lack of clear policy and guidelines, lack of framed and programmatic research agenda, lack of voluntary participation and awareness of patients were the ones pointed out by most participants (n=11) in relation to operational obstacles and poor research governance. Translating animal research to human clinical trials demands commitment from researcher, partners and government. As noted by the study participants:

One participant gave emphasis on the need for a clear policy which guides the conduct of translational research that *"No clear policy and central coordination…so the medical associations, association of the biologists, the veterinarians should come together and doing some policy issues governing this [translational study]. I think the policy issue is very important for such activities"* (A3, preclinical trial researcher).

"...Lack of a clear cut guideline on how to do a clinical trial on traditional medicine is the major challenge because we cannot adopt the guideline for conventional approaches…." (A14, preclinical trial researcher).

"When you conduct a research it is not only the resources but also research management by itself is a problem. So if you have research funds you get from somewhere else unless there is a smooth research financial management system which motivate the researchers…everybody will lose its hope and their interest in research in the next phase" (A15, clinical trial researcher).

"What I can say is that…probably low or poor commitment to translate the research finding into the product. When I say commitment, commitment from the researcher. Many researchers are just complaining…by the availability of reagent, consumables, laboratory facilities…the leadership from respective institutions or universities and the government in general. I underlined that it is a low commitment at each level if you are committed to change the preliminary product into the final product to be useful for public service then you have to committed in terms of working, extra working hours, you have to work day and night including weekend and you have to look for different opportunities and possibilities to get all the reagents and consumables" (A2, preclinical trial researcher).

"...If you want to purchase a chemical let us say from abroad, it will take you three years by that time everything is over. Now there is much improvement but still we have to make it faster" (A15, preclinical trial researcher).

"...May be related to an awareness of participants…most patients when they told us about clinical trials they think they are going to die they would not like to get consent to participate in clinical trials" (A16, preclinical and clinical trial researcher).

"...Getting patients who are voluntary to participate is also another difficulty...they do not have the culture of voluntary participation in a clinical trial unless you have a financial incentive for it" (A1, clinical trial researcher).

Theme 4: Lack of collaboration

Lack of interdisciplinary collaboration among different professional groups in different institutions at the local and international level, was perceived by respondents to hinder the practice of translating animal research into human trials. Respondents identified a number of features including poor research governance and bureaucracies, minimum preparedness and awareness of the research community, delay in the approval process and communication barriers that hindered effective

collaborative working relationships and practices at international level. As stated by the study participant:

"…We need to enhance collaboration with expertise and resources…from outside with certain cautions in terms of not abusing the human trials in general. But the research governance, bureaucracies like delay in the approval process, the preparedness and awareness of the research community, poor facilities and communication are actually hindering in terms of collaboration because many of the collaborators need a kind of swift, smooth…like for instance in terms of the approval process of research protocol, it took like a year in Ethiopia and they don't want to work with Ethiopian collaborator because of this. So once we can actually improve this research governance and the ethics and regulatory approval process there is also an opportunity just to draw resources from outside so that we can collaborate and hasten product development as well as translate the products into human or animal application" (A10, clinical trial researcher).

Nine participants suggested that translating animal research into human trials needs a multidisciplinary and inter-sectoral collaborative work. Therefore, there should be multi-disciplinary collaboration among biologists, medical professionals, veterinarians, chemists, health officers, policy-makers, social scientists and communities, and companies, which ultimately produce and sell that product to the population. The researchers or professors from basic science or biomedical research area are initiators and part of the whole research process. As noted by the study participants:

"Although researchers are the main actor who come up with the idea and the compound, translational research needs involvement of many actors: the government, biomedical researchers, chemists, physicians, social sciences scientists, nurses, laboratory technicians, immunologists from animals and human side" (A17, preclinical and clinical trial researcher).

"*I think it is a concerted effort. It is not something that is left for one institution, of course the government has given that the mandate for EFDA [Ethiopian Food and Drug Authority] in Ethiopia to regulate and Armauer Hansen Institute to lead clinical trial activities. However, it doesn't mean that it has to be done there, but…the teaching and research institutions, private and government hospitals, veterinary colleagues and individual scientists should be involved...So that they can work together from animal to human side…that is in terms of doing the study otherwise in terms of*

stakeholders acting around it, there are a number of different stakeholders we need to have DSMB, IRB approval, investigator team members, monitor, if there is a need for sponsor, if you are soliciting some funding (funder), and CRO. So all those actors need to be there" (A7, preclinical and clinical trial researcher*).*

Theme 5: Lack of reproducibility of results

Lack of reproducibility of results was also considered as a major bottleneck for translating animal research into human trials. Poor experimental design, poor quality animal experiment, nature of diseases, animal model specifics, differences between animal and human genetic make-up, inappropriate statistical analysis, and anatomical and physiological species difference were seen as contributing factors to lack of reproducibility and replicability of findings in which an agent that is found effective in animal studies might not be effective in human studies. This was only mentioned when the interviewer asked participants in a follow-up question to give reasons for lack of reproducibility. As reported by the interviewee:

"*The major bottleneck is the lack of reproducibility and replicability of findings…a drug or vaccine that is found effective in animal studies might not be effective in human studies. It could be because of inappropriate statistical analysis or poor experimental designs. So had the research been designed well it could have an effect in the clinical studies…although the assumption is…that there is…a predictive validity or a face validity between the disease you model on animals and the disease that is in humans…mostly you don't see the agent be effective in human studies. It could be related the nature of the disease. So in some diseases…you see a positive effect in both studies in another studies you do not see similar findings. So lack of reproducibility is the major challenge in the translating animal research into human trials"* (A8, preclinical and clinical trial researcher).

Theme 6: prolonged ethical and regulatory approval processes

Six interviewees expressed their dissatisfaction in their work in translating animal research into human clinical trials because of the delay and very stringent working environment in ethical and regulatory review and approval processes. The resulting slow and excessively strict ethical and regulatory approval process prevented efficient research conduct. The interviewees mentioned that the time taken for one research protocol to be approved ranged from one to two years. This has contributed a lot in lowering the chance to get external funds for a study or to attract donors and

collaborators, because funders or donors are eager to give you the money if you are lagging behind because of the ethical process, unnecessary delay in review process could result in donors losing their interest. Therefore, we have to exploit such opportunities by improving the research process and making ethical and regulatory approval a bit faster. A participant stated that:

"…I do not think that since there is no capacity and experience even ethically they will allow you to translate animal research into human trials,…I was involved in one study which was on edible mushroom…and we proved it in animal that was for liver cancer and the intention was to translate that into human and we did not succeed the level of ethical approval that was needed" (A7, preclinical and clinical trial researcher).

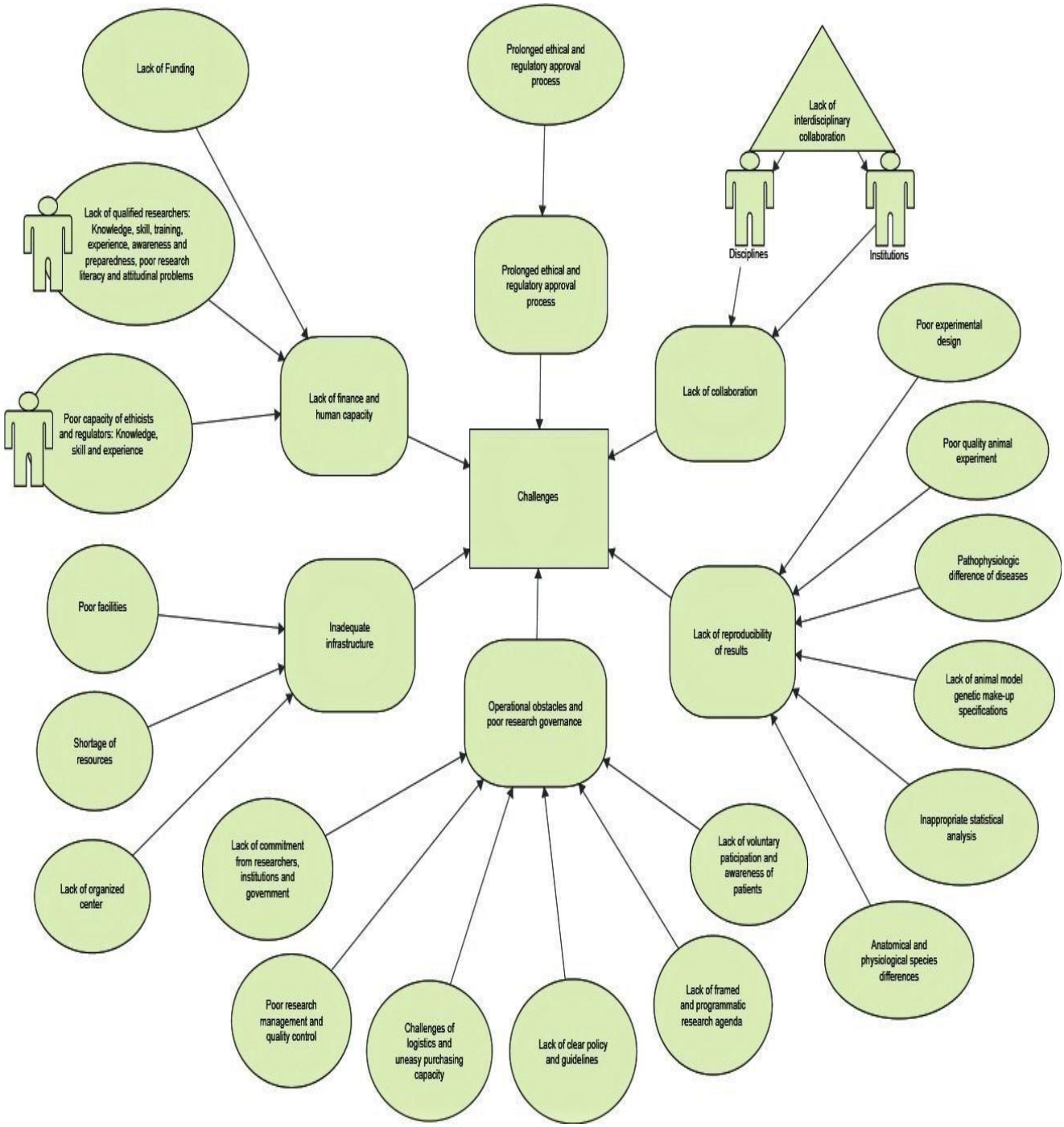

Figure 1: Concept map shows themes and sub-themes for challenges that hinder translating animal research into human trials

Table 2: Summary of themes emerged as challenges of translating animal research into human trials**.**

Themes	Frequency (number of participants mentioned the theme as challenges)	Sub- themes
1. Lack of finance and human capacity	13	✓ Lack of funding ✓ Limited capacity of researchers (knowledge, skill, experience, awareness and preparedness), attitudinal problems, lack of physicians' interest ✓ Limited capacity of ethics committee and regulators in terms of knowledge, skill, experience
2. Inadequate infrastructure	11	✓ Poor facilities (e.g. accredited laboratories) ✓ Shortage of resources ✓ Lack of organized center
3. Operational obstacles and poor research governance	11	✓ Lack of commitment from researchers, institutions and government ✓ Poor research management and quality control ✓ Challenges of logistics and purchasing process ✓ Lack of clear policy and guidelines ✓ Lack of framed and programmatic research agenda ✓ Lack of voluntary participation and awareness of Patients
4. Lack of collaboration	9	✓ Lack of inter-disciplinary collaboration
5. Lack of reproducibility of results	6	✓ Anatomical and physiological species differences ✓ Inappropriate statistical analysis ✓ Lack of animal model genetic make-up specification ✓ Pathophysiologic difference of diseases ✓ Poor experimental design ✓ Poor quality animal experiment
6. Prolonged ethical and regulatory approval processes	6	✓ Prolonged ethical and regulatory approval processes

5.2.2. Opportunities for translating animal research into human trials

Theme 1: Growing infrastructure and resources

Six interviewees mentioned that these days there are many universities with many postgraduate studies in various disciplines and institutions that are mandated to conduct research, which should be taken as an enabling factor. Since most of the institutions are good in basic sciences if provided special training, they can turn to be efficient in conducting translational research. There are also a motivation and support from Ministry of Innovation and Technology for institutions to be a center for problem solving research rather than a simple office for academic exercise. According to the interviewees, there are also institutions like CDT-Africa, which provide education, training, and capacity building for researchers to be engaged in translational research and this can be taken as a good start and which can be considered as enabling factor. As stated by the study participants:

"…Institutions like the CDT Africa a world bank initiative dedicated to do this kind of translational study…are enabling environment and now more than ever we have got a wonderful environment to conduct this [translating animal research into human trials]" (A7, preclinical and clinical trial researcher).

*"…In the Ethiopian context, the two research communities are found either in a research institution or in academic institutions/universities. Now, there is a developing potential, especially in the universities because those universities have science faculties, health colleges, and tertiary hospitals. Therefore, we need to have a somewhat integrated planning so that we can exploit the maximum of the academic community there and then the research idea that can be developed from biomedical field can easily be translated into human or animal testing. So…particularly the research community in research institutions and in academic areas needs actually to work together and they need to have a common platform after all…that can connect them regularly so that they can read each other" (*A10, clinical trial researcher).

The interviewees said that though there are limitations now a days there are growing or better facilities, many tertiary hospitals are now under establishment/ development than previous years. As reported by the study participant:

"I would say at least the experience that I have, at Addis Ababa University; there is phase -1 clinical trials unit, at Armeaur Hansen research institute; there is the whole ward that dedicated for phase- 1 clinical trial unit and internationally accredited laboratory. …These days, there are wonderful infrastructure wise enabling environment" (A7, preclinical and clinical trial researcher).

Five of the interviewees mentioned that the availability of high diversity of medicinal plants, microbes, to some extent availability and use of animal model following proper ethical procedure and large human population in which many of them harboring many infectious and non-infectious diseases could be taken as a big opportunity for translating animal research into human trials. Besides, the existence of multi drug resistance to the drugs being used, inaccessibility of modern medicine to most of the local communities and availability of indigenous knowledge on the use of traditional medicines for curing of diseases is among the enabling factors stated by the interviewees. As noted by the study participants:

"…No full accessibility of modern health cares. So, one approach is to strengthen research on traditional medicine, including the clinical trial because it's cheap, easily accessible, and it can serve as a means of generating income…" (A14, preclinical trial researcher).

"I think there are…opportunities like the existence of multidrug resistance to the drugs that has been used. So one of the ways forward is to investigate and come up with the new drug to replace those drugs which drug resistance are developed" (A3, preclinical trial researcher).

Four interviewees mentioned that currently, there are opportunities for getting funds at international level and companies are interested to support the initiation of traditional medicine clinical trial. In addition, the Ministry of Innovation and Technology, and Ethiopian Biotechnology Institute are nowadays giving emphasis on product-oriented research and are allocating better fund as compared to funds made available in the previous years.

"Though competitive there are still research funds to get to clinical trial, so what is expected from us is to write the grant proposal otherwise it may not be as difficult as used to be in the past" (A16, preclinical and clinical trial researcher).

Theme 2: Improved human capacity and better administrative processes

Most interviewees indicated that these days researchers have better capacity in terms of knowledge, skill, training, experiences, and awareness as compared to a few years back. Universities have produced higher number of trained researchers and as a result, there is a growing interest of scientists and growing work force in biomedical fields or health related research. In addition, the quality of research now is improving. As noted by the study participants:

"…Opportunity for training, capacity building and education of researchers to be engaged in translational research you can take your clinical trial program offered by CDT-Africa and funded by several projects…. So we can consider these as enabling factors" (A8, preclinical and clinical trial researcher).

"…Well, currently it looks there are a lot of opportunities for clinical trials to be considered we are building the capacity and awareness of health professionals through trainings…on how clinical trial is conducted. So I am sure these days most of them become interested in clinical trials" (A16, preclinical and clinical trial researcher).

"Well, I would say the opportunity now is…if you take during my old time it was very difficult, now the attention towards education and research is far better than it used to be in the last two or three decades back" (A15, clinical trial researcher).

Moreover, interviewees mentioned that very recently there are better administrative processes including, supportive rules and regulations, initiations to speed-up ethical and regulatory approval, and the government is giving due attention to problem-solving and product-oriented research. As noted by a study participant:

"…The ethical approval process is being improved…we are working on that how to correct the problem with the ethical committee used to have…even the regulatory approval process…is going to be shorten I believe" (A16, preclinical and clinical trial researcher).

Another study participant stated that;

"The one I would say is there are supportive…rules and regulations issued by the government. …Now the mandate and the proclamation are out there so it is up to the scientist and those other stakeholders to engage" (A7, preclinical and clinical trial researcher).

One respondent also stated that "*There are enabling environment that has been worked out which helps if you really want to know the fact that a lot of preclinical study has been done before and having a database on those once, there are some initiatives to develop a database as well. It is something we can also count on experience from other country China, India, Nigeria*" (A7, preclinical and clinical trial researcher).

Theme 3: Initiatives for collaborations

Interviewees mentioned that one-health initiative at the national and international level could be considered as an enabling environment and it can facilitate collaboration by creating a platform for experts to meet and work together. As reported by the study participant:

"It is the good way and now we are initiating to work together with National Veterinary Institute (NVI), EPHI, AHRI and Ethiopian Biotechnology Institute…to develop a product for human and animal use. We already initiated but it is under establishment and we are working to make a strong collaboration because we have to share our expertise or facilities if something that NVI is by far better than others…." (A2, preclinical trial researcher*).*

Theme 4: Similarities between species

One respondent said that there is a similarity between animals and humans in terms of biology, mechanism of actions of drugs and most diseases are transmitted between them. This can be taken as an opportunity for conducting product-oriented research on animal model and to be used on humans.

Figure 2: Mind map that shows themes for the opportunities for translating animal research into human trials

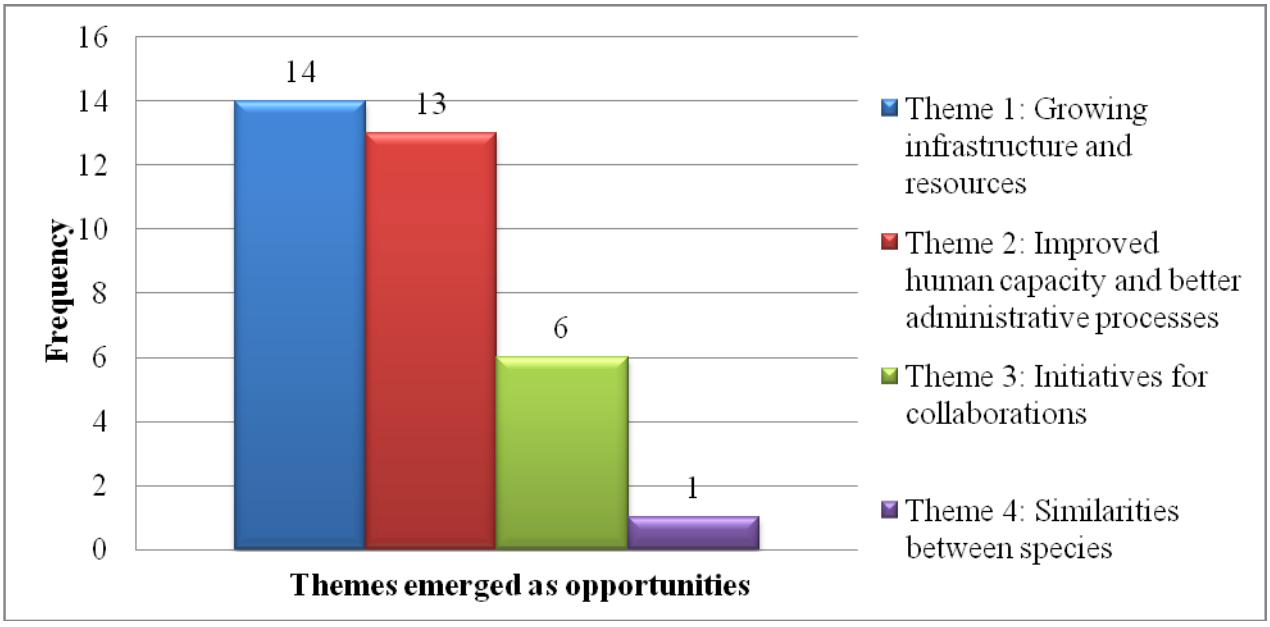

Figure 3: Themes and the number of participants mentioned each theme as opportunities.

6. DISCUSSION

The goal of translational research is to bring biomedical knowledge from the laboratory to clinical application and therapeutic products (Enna and Williams, 2009, Kotarba *et al.*, 2013). Previous attempts such as "clinical pharmacology" and "experimental medicine" have not been very successful in moving from science to commercialization and the patient's bedside (Collins, 2011). To move from animal studies to clinical trials is a complicated process and depends on the cooperation of research institutes and companies, the settling of ownership and property rights, and the creation of a well-developed business model (Chen, 2009).

The identified challenges concerning translating animal research into human trials are summarized into six themes: lack of finance and human capacity, inadequate infrastructure, operational obstacles and poor research governance, lack of reproducibility of results, lack of collaboration, and prolonged ethical and regulatory approval processes. On the other hand, the enabling factors that were perceived for translating animal research into human trials are summarized into four themes: growing infrastructure and resources, improved human capacity and better administrative processes, initiatives for collaboration and similarities between species.

The present study showed that lack of funding and human capacities were among the most frequently raised constraints that hinder translating animal research into human trials. Most respondents reported that they were frustrated to involve in translating animal research into human trials because of limited local research fund and highly competitive international funds. This contributed towards increased mobility of highly talented staff to Western countries like Europe and America in search of conducive research environment. Similarly, little local funding and competitive international funding have been reported as a barrier to conduct locally initiated clinical trials in previous study conducted in Ethiopia (Franzen *et al.*, 2013). However, two preclinical trial researchers from the present study indicated that funding was not a problem; instead, it was a financial management problem. This difference in perception related to funding among the respondents might be due to variation in the type of study they were involved, experience and financial management system they have. Successful translational research requires adequate fund, an important part of which is government funding (Zhou *et al.*, 2013). Most academic institutions do not have an adequate budget to support discovery and development programs (Parrish *et al.*, 2019)

and it is a well-acknowledged fact that it is almost impossible for academicians to procure sufficient competitive grants to bring a drug or a test to the clinic and comply with all the testing procedures necessary to meet regulatory requirements (Hörig *et al.*, 2005). For a research institute to be able to do translational research from bench to bedside, it had to cooperate with hospitals for clinical trials, and for later stage trials and product development, taxpayers' money was not enough to support its work; thus, a partnership with industry was envisioned to address the financial problem efficiently. Hence, it has become a strategy to invite industry to get involved earlier in the translational research process (Ma *et al.*, 2014). Moreover, this study showed that these days the government gives due attention to research and allocates better money for product oriented research than that were used in the previous years. This may be because of the reason that previously a lot was done on preclinical studies and now it is time to move to the next phase.

Many of the respondents also reported that challenges in getting or maintaining qualified experts in terms of knowledge, skill, experience, training, and awareness. This is in line with a mixed method study conducted in Australia, which states that both preclinical and clinical researchers were frequently lacking confidence in research translation skills and knowledge (Lynch *et al.,* 2018). Translational researchers need to have multidisciplinary knowledge and capability (Zhou *et al.*, 2013). Those translation investigators who are dually trained in scientific laboratories and clinical settings are very important personnel to link the information both from bench and bedside, but they are "rare species" (Chen, 2009). Interviewees from the present study reported that translational research or medicine needs to be incorporated into the national educational curricula to cultivate trained and multidisciplinary translational researchers and further suggested that there should be financial and non-financial incentives, rewards, and recognitions given to them at national level. A flexible framework for performance assessment that tracks progress and incentivizes fruitful activities is very important for cost-effective translational research (Zhou *et al.*, 2013). Trial training, knowledge sharing, and experience exchange are key enablers for increasing awareness, confidence, and motivation. Training was viewed as important for awareness and encouraging staff to consider their workplace challenges in a more enquiring light. Knowledge sharing boosts a researcher's confidence that trials are achievable and experience exchange is important for raising professional standards and dispelling what one respondent termed 'pseudo-confidence' meaning to continue working in a suboptimum way because knowledge of more rigorous methods is lacking (Lynch *et al.*, 2018).

Interviewees particularly stressed on attitudinal problems of researchers that misunderstood successful completion of a project as production of publications only. It is a common practice that promotion of staffs in academic institutions is measured by the number of high quality publications, not by the number of patents received. It was also pointed out that most of the studies, especially preclinical studies, were conducted by undergraduate, Masters or PhD students. However, after graduation of the students, no one is there to continue the work by taking it to the next level. This is in line with a finding conducted in USA, which stated that academics are rewarded for being the first to describe a scientific discovery (to obtain tenure, professors must demonstrate leadership in their field through grant funding, a strong teaching record, and, most importantly, high-quality publications and recognition by national and international scholars) and not for preparing a successful IND application to the FDA and the risk of delaying or perhaps preventing their promotion forces academics to pursue drug discovery and development as a side activity (Parrish *et al.*, 2019). Despite the apparent importance of translation, translating beyond publication was not always a priority for the research team that tended to focus on conducting new research and publishing (Lynch *et al.*, 2018).

The other theme that emerged as a challenge was inadequate infrastructure, including poor facilities and shortage of resources and lack of well-organized center. This was supported by a study conducted in Ethiopia, which stated that lack of materials; infrastructure and laboratory facilities were thought to reduce the number and scope of trials (Franzen *et al.*, 2013). The present finding suggests the establishment of a well-equipped center specialized only for translational studies. Provision of training and education at Masters and PhD levels in clinical trials and translational research without creating an appropriate research center for the graduates to be engaged in such researches is meaningless, and they will end up in universities only teaching clinical trials courses. However, a series of education and skills development trainings have been given to address the reported needs of both preclinical and clinical researchers regarding research translation (Lynch *et al.*, 2018).

Operational obstacles and poor research management, such as poor commitment from researchers, institutions and the government, poor financial management, lengthy and complex logistics and difficult purchasing process, lack of clear policy and guidelines, lack of framed and programmatic research agenda, lack of voluntary participation and awareness of patients were identified to

influence the practice of translation of animal research into human trials. Research has to be framed and planned with enough resources, facilities, and experts at the beginning. Correspondingly, a study conducted on barriers and enablers of implementation of the local investigator initiated clinical trials in Ethiopia showed that the majority of serious operational difficulties such as problems with trial management, burdensome administration, and difficulty purchasing supplies, problems with setting up and running laboratory tests occurred during the start-up stage of trial conduct (Franzen *et al.*, 2013).

The study illustrated that interviewees perceived lack of interdisciplinary collaboration was a challenge that hindered translating animal research into human clinical trials. Other studies also found out that lack of interdisciplinary collaboration between basic and clinician scientists and with other professional groups were considered to hinder the practice of translational research *(*Kotarba *et al.*, 2013, Zhou *et al.*, 2013). The present finding suggests that translation of animal research into human trials is the responsibility of many actors from different disciplines. Multidisciplinary collaboration at national and international level can create a platform for scientists from different background and direction to come together, discuss on prioritizing issues, and read each other rather than conducting pieces of repeated researches here and there in different institutions. Translational research needs two-way or multi-way dialogue between scientists and clinicians, and cooperation between academia and industry (Chen, 2009). This was also supported by other studies that interdisciplinary collaboration was supposed by scientists as important to facilitate translational research practices (Kotarba *et al.*, 2013, Zhou *et al.*, 2013) by providing chances for knowledge exchange (Wainwright *et al.*, 2006), offering distinct forms of expertise (Zhang, 2011), and creating a working environment which encourages communication and co-operation between different scientists (Fudge *et al.*, 2016). Collaboration was seen as being best achieved through multi-disciplinary teams, working throughout the entire research process (Kotarba *et al.*, 2013). However, interviewees from the present study identified different internal factors such as poor research governance, poor facilities, awareness and preparedness in the research community, prolonged ethical and regulatory approval process and communication barriers that hamper collaboration particularly at international level. This is also supported by findings which shows the identification of a number of factors by scientists that hindered effective collaborative working relationships and practices such as previous professional groupings who do not want to share experiences beyond their group (Long *et al.*, 2014) and poor leadership skills of team managers/leaders and institutional

arrangements (Fudge *et al.*, 2016). Traditional barriers between academia and industry is accompanied by conflict of interest issues (Chen, 2009). All of these institutions in the same network make bench to bedside interactions possible, but conflict of interests remained a problem for cooperation and affected the stabilities of the network (Ma *et al.*, 2014).

The study has illustrated that findings found to be effective in animal model were not effective in human studies as noted by respondent who had experience in translating animal research into human trials. The reason could be due to anatomical, physiological, and genetic difference between animals and humans, poor experimental design, inappropriate statistical analysis, and nature of diseases, which contributes to irreproducibility and lack of replicability of findings. Similarly, irreproducibility of animal research findings due to methodological flaw including poor experiment, design and inappropriate statistical analysis have been reported as one of the challenges contributed to low animal to human translational success rates in previous qualitative study conducted with directors of academic programs in USA (Parrish *et al.*, 2019). Another Chinese case study from the researchers in the Zhao laboratory during clinical trials showed that the drugs that tested effectively in animal studies were not at all effective in the clinical trials with humans because the patients' conditions were much more complicated than simulated in the animal studies (Chen, 2009). These animal models are precisely defined in the context of a uniform genotype and in a uniform environment but stand in stark contrast to humans who have a comparatively varied genetic composition, highly variable diet, and exposure to an array of environmental stresses. Concerns regarding the translatability of animal models are further emphasized by well-known structural and functional differences between human and animal models. For example, a mouse heart beats at around 600 bpm compared to 70 bpm in humans (Lal *et al.*, 2016). Such differences can complicate the interpretation of results from animal models and their applicability to drug testing and human clinical trials.

This study also identified that the delay in ethical and regulatory processes because of limited qualification and experience of ethics committee members or unreasonably strict approval process by the committee as a barrier for translation of studies conducted on animals into clinical trials. This was supported by qualitative study conducted in Ethiopia, which stated that slow regulatory and ethical approvals due to complex and unclear guidelines, limited ethical review capacity, poor-quality submissions made it very difficult to investigate novel interventions and it was not

uncommon for grants to expire before all approvals were in place (Franzen *et al.*, 2013). Similarly, a survey of senior researchers working in USA Medical Schools and Academic Health Science Centers found that 38% of those surveyed identified complex regulatory requirements as particularly challenging for translational research, thus limiting the success of biomedical innovation being translated into benefits for patients (Campbell *et al.*, 2001). Chinese study group conducting research on stem cells, revealed that regulation was complicated by numerous, overlapping regulatory jurisdictions inadvertently promoting inconsistency and minimal conformity with the law, resulting in scientists feeling powerless to change the system (Zhang, 2011). Ethical and social implications of scientific advances were perceived to add an additional layer of complexity to translational research. Scientists working on stem cells as a potential therapy for leukemia (Chen, 2009) and diabetes (Wainwright *et al.*, 2006) reported making a deliberate effort to follow strict regulatory processes to ensure acceptance and legitimacy of their research (Chen, 2009). The present study also highlighted the initiation to identify the problems causing delay and complexity of ethical and regulatory approval processes to make it faster as mentioned by few respondents.

On the other hand, growing infrastructure and resources was the first theme emerged as opportunity for translating animal research into human trials. This includes many universities with many post graduate studies in various disciplines and institutions like CDT-Africa that are mandated to conduct research and which provide education, training, and capacity building for researchers to be engaged in translational research, motivation and support from Ministry of Innovation and Technology for institutions to be a center for product oriented research, better facilities, the availability of high diversity of medicinal plants, microbes, availability and use of animal model and large human population in which many of them harboring many infectious and non-infectious diseases, the existence of multi drug resistance for the drugs being used, inaccessibility of modern medicine to most of the local communities and availability of indigenous knowledge on the use of traditional medicines for curing of diseases is among the enabling factors stated by the interviewees. This shows the direction to that could help and enhance the practice of translating animal research into human trials in Ethiopia.

Moreover, improved human capacity and better administrative processes was mentioned as opportunity. This study shows these days researchers have better capacity in terms of knowledge, skill, training, experiences, and awareness as compared to few years back. In addition, there is

growing interest of scientists, growing work force in biomedical fields or health related researches and better quality of research. This may be happening now because of the world education is geared towards e-learning, scientists may get trainings and education through online courses or scholarships, and they can increase their understanding on importance translational study. The present study also illustrated that there are better administrative processes including supportive rules and regulations, initiations to speed-up ethical and regulatory approval, and the government is giving due attention to problem-solving and product-oriented researches. Therefore, this could motivate scientists to enhance their interest to work on translating animal research into human trials.

This study revealed that despite the challenges of collaboration, there are now initiatives like one health and initiations for collaboration among research institutions. Hence, this could create a platform for scientists from different background to share their knowledge, experience, and skills in research and to discuss on common issues. Interviewees suggested that this should proceed beyond the initiation.

This study also identified that the similarities between species (between animals and humans) such as similarities in biology and mechanism of action of drugs and other zoonotic diseases as an opportunity for conducting product-oriented research on animal model and to be used on humans. This is also supported by other literature, which stated, as the use of animals is not only based on the massive similarities in the biology of most mammals, but also on the fact that most human diseases often affect other animal species. It is particularly the case for most infectious diseases but also for very common conditions such as Type I diabetes, hypertension, allergies, cancer, epilepsy, myopathies and so on. The mechanisms are often also so similar that 90% of the veterinary drugs used to treat animals are identical or very similar to those used to treat humans (Barré-Sinoussi and Montagutelli, 2015).

7. STRENGTHS AND LIMITATIONS OF THE STUDY

7.1. Strengths

To my knowledge, this is the first empirical thesis study investigating the challenges and opportunities for translating animal research into human trials in Ethiopia. This study may provide a compelling insight on challenges and opportunities for translating animal research into human trials for scientists in Ethiopia who are often unheard about that. Participants were from one of the major research and academic institutions, conducting research that contributes to health in one or another way.

7.2. Limitations

Although this study highlights a number of very important issues, there are also limitations. Responses of participants may have been influenced by author's involvement. As a formative study, the sample size was small, the sampling was purposive, and the findings may be context specific unlike that of quantitative study, which focuses on the generalizability of findings. The participants in this study were only researchers from preclinical and clinical trials area that were purposively selected, could not represent the views of other stakeholders involved in translational research..

8. CONCLUSION AND RECOMMENDATIONS

This study attempted to identify the challenges that hinder translation of animal research into human trials. Several challenges summarized in six themes were identified: lack of finance and human capacity, inadequate infrastructure, operational obstacles and poor research management, lack of collaboration, lack of reproducibility of results and prolonged ethical and regulatory approval processes. It also highlighted the existing enabling environments for translating animal research into human trials. The major existing opportunities identified by the respondents were synthesized into four themes: growing infrastructure and resources, improved human capacity and better administrative processes, initiatives for collaboration and similarities between species (animal and human). The study found that these identified characteristics/features are of high importance either to hurdle or enable the practice of translating animal research into human trials.

Based on the above conclusion the following recommendations are forwarded:

- Infrastructures should be in place by the government for example good standard facilities such as hospitals, clinics, laboratories should be equipped up to the standard and has to be certified with calibrated equipment, and documented standard operating procedure.
- The government should allocate a sustained funding streams and financial support dedicated for translating successful animal experiments into clinical trials.
- Expanded training courses at different levels is required and translational research should be incorporated into educational curriculum to introduce researchers to the concept of translating animal research into human trials in particular at early stage and to build their capacity.
- The government needs to be committed on encouraging research that has to be translated from animal model into human trials.
- Multidisciplinary collaboration among different professional groups needs to be enhanced at individual, institutional, national and international levels to discuss on gaps, share experiences and resources to make the research work sustainable and fruitful.
- There should be efficient research governance while researchers conduct a research and resources should be used efficiently. All research activities should be documented, recorded, evaluated regularly, and aimed at developing a product.
- While writing proposals, it has to be evaluated seriously from the availability of multidisciplinary experts and different institutions, availability of reagents, consumables and laboratory facilities.
- Dedicated leadership at each institution and investigator level is required.

- Researchers need to do high quality standard animal research by using a well-designed methodology.
- The ethical and regulatory approval process has to be highly improved by the ethics and regulatory bodies
- Public awareness on clinical trials needs to be improved through community outreach and engagement program to enhance the interest of the community to join in hands with the researchers so that for the future generation better therapeutics could come.
- Negative result of research should be considered as a good experience by researchers and it has to be distributed to other researchers, all the difficulties/ challenges and the outcome. It is a lesson for other researchers.
- There should be a kind of financial and non-financial incentives and recognitions for the researchers who are successful on translation of animal experiments into human trials at national level
- Clear guidelines on how to conduct clinical trial on traditionally claimed medicinal plants needs to be developed by policy makers.

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10. ANNEXES

Annex-1. Information Sheet

Greeting (Good Morning/ after noon)? I want to thank you for taking your precious time to meet with me today. My name is _____. I am currently MSc student in Clinical Trials and I am doing my thesis for the partial fulfillment of master's degree in Clinical Trials at CDT- Africa, College of Health Sciences, Addis Ababa University. I would like to collect information from you by in-depth interview about "Translating animal research into human trials in Ethiopia: Challenges and opportunities". Objective of the study is to investigate the challenges and opportunities of translating animal research into human trials in Ethiopia. The interview will take about 45-60 minutes. I will be recording the interview session because I do not want to miss any of your ideas and comments. Although I will be taking some notes during the interview session, I cannot possibly write faster enough to get it all down. Because we are on recording, please be sure to speak up loud and relax so that I do not miss your important and valuable answers. Interviewing will take place in a private office/room. We would like to assure you that this privacy would strictly be maintained throughout. A code will be used to identify your participation. Your name will not be written on this form and will never be used in connection with any of your responses to any of the questions. We want to assure you that any information we will include in our report does not identify you as the respondent. Remember, your participation is voluntary and you do not have to talk about anything you do not want to and you may end the interview at any time, if any dislike conditions happen during the interview. The study does not incur any risks because of your involvement. Please be informed that there is no any direct benefit in a form of incentives or money attached to your participation in this study. Please, be aware that all information you provide us is valuable and very important to identify the challenges and opportunities to enhance translation of experimental animal findings into human trials for future human health improvement. If there are things that require clarification, you have the right to ask. For any other additional information about the study, please contact the principal investigator and her advisors by the following address:

Name, Address and **Tel number** of **PI**: Name: Dr. Askale Abrhaley, CDT-Africa, Tel: 0928423688.

Advisors:

1. Prof. Mirutse Giday, Aklilu Lemma Institute of Pathology, Tel: 0911882912.
2. Prof. Asrat Hailu, College of Health Sciences , Tel: 0911-480993

Should you be willing to agree to participate in this study, I would like to thank you for your time and for the information, you are willing to share with me.

Annex-2: Informed Consent Form

In signing this document, I am giving my consent to participate in the study entitled "Translating animal research into human trials in Ethiopia: Challenges and opportunities". I have been informed that the objective of this particular research project is to investigate the challenges and opportunities of translating animal research into human trials in Ethiopia. I am also informed that the study will be conducted through an interview I am going to respond to this question by answering what I know concerning the issue. I am also informed that the information I gave will be treated confidentially. I have also been informed that I can refuse to participate in the study or not to respond to question if I am not interested. Furthermore, I have been informed that the research does not incur any risk and no money or incentives will be given for my participation in the study. I understand that the results of this will have some input to identify the challenges and opportunities of translating animal research into human trials for future health improvement. I have assured that the right to ask information that is not clear about the research before and or during the research work and to contact:

1. Dr. Askale Abrhaley (Tel: 0928423688)
2. Prof. Mirutse Giday (Tel: 0911882912)
3. Prof. Asrat Hailu (Tel: 0911-480993)

I have read this form, or it has been read to me in the language I comprehend and understood the condition stated above, therefore, I am willing and confirm my participation.

Are you willing to participate in this study? 1. Yes 2. No
Interviewee Code No. _____ Signature _____ Date_____

Thank you for cooperation and spending your time.

Annex-3. Interview Guide

A. Demographic background

- ✓ What was your area of expert?
- ✓ For how many years have you been working in preclinical trials/ animal research or clinical trials?
- ✓ In how many pre-clinical/clinical trial research projects have you been involved as a principal investigator?
- ✓ What were your areas of research in terms of disease/pathogens?
- ✓ What was tested in your preclinical or clinical trials: drugs, vaccines, devices, other interventions, etc.?
- ✓ In which phases of trials have you been involved?

B. Questions

1. What do you understand by the term, translational research?
2. Have you been involved in translating animal research into human trials? If **Yes**: drugs or vaccines?
3. What is your opinion on the proportion and quality of animal research versus human trials in Ethiopia?
4. Do you think that there is an original animal research initially done in Ethiopia that has been translated to human trials/clinical trials so far? If **Yes**: when? And how many?
5. What do you think are the challenges, which hinder translating animal research into human trials?
6. Whom do you think that the responsible body for translating animal research into human trials/clinical trials?

   What do you thing about the possible enablers /opportunities for translating of animal research into human trials?
7. What recommendation would you suggest to enhance the practice of translating animal research into human trials?
8. Do you have anything to add?

This interview guide only focuses on the data that will be presented in this thesis.

Annex-4: Data Analysis Procedures, Actions Taken, and the Outcomes (Visual Displays)

Step 1: Data cleaning was conducted

- ✓ The collected written and audio-recorded data were checked for completeness, accuracy, clarity, and consistency.
- ✓ Transcription was done and the data was compared with the note taken during data collection

Step 2: The data was uploaded into Nvivo-12

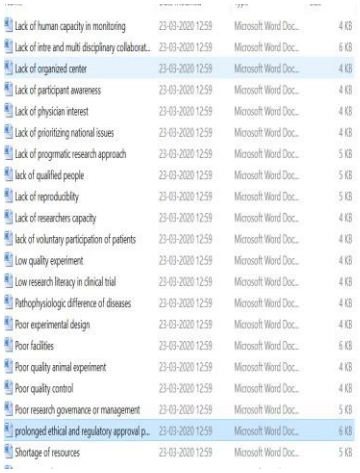
Step 3: The data was reorganized (using auto-coding)

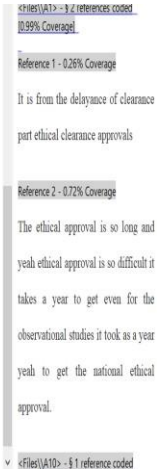
- ✓ The uploaded data was sorted out by interview question to bring together responses of all the respondents to every specific question.

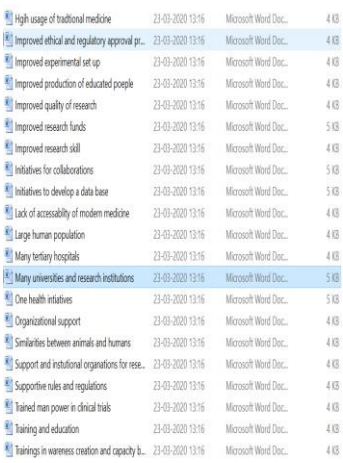
Step 4: Data exploration was conducted (using query command)

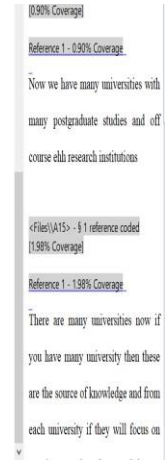
- ✓ Word cloud for the most frequently raised word and word search query (word tree)

Step 5: Started coding relevant information in the data and saving in the code book with description









Codebook for nodes under challenges of translating animal research into human trials

Name	Description	Files	References
Challenges	This is a container for the themes or parent nodes and child nodes coded here to represent the challenges that hinder translating animal research into human trials. It is an anchor code for my first research question which is "What do you think are the challenges which hinder translating animal research into human trials?"	0	0
Inadequate infrastructure	This is the theme for child nodes related to facilities, resources and centers	0	0
Lack of organized centre	Lack of organized centres For example there are studies done repeatedly here and there and organizing these things together is very weak.	2	4
Poor facilities	Poor facilities in terms of furnished and well-equipped laboratory and clinics that enable researchers to conduct specially a clinical trial from phase 1 to 3.	9	19
Lack of accredited laboratory	So if you want to do experiments on animal models that laboratory has to be GLP accredited but there are no accredited laboratories	1	2

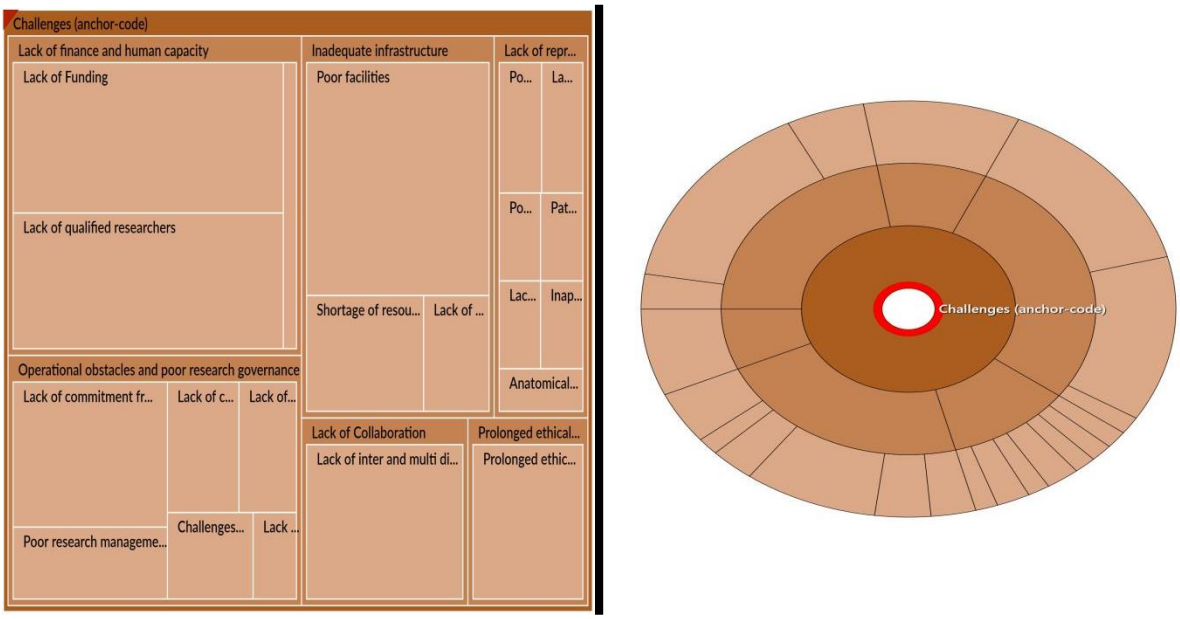
Translating animal research into human trials: Challenges and Opportunities

Codebook for nodes under opportunities

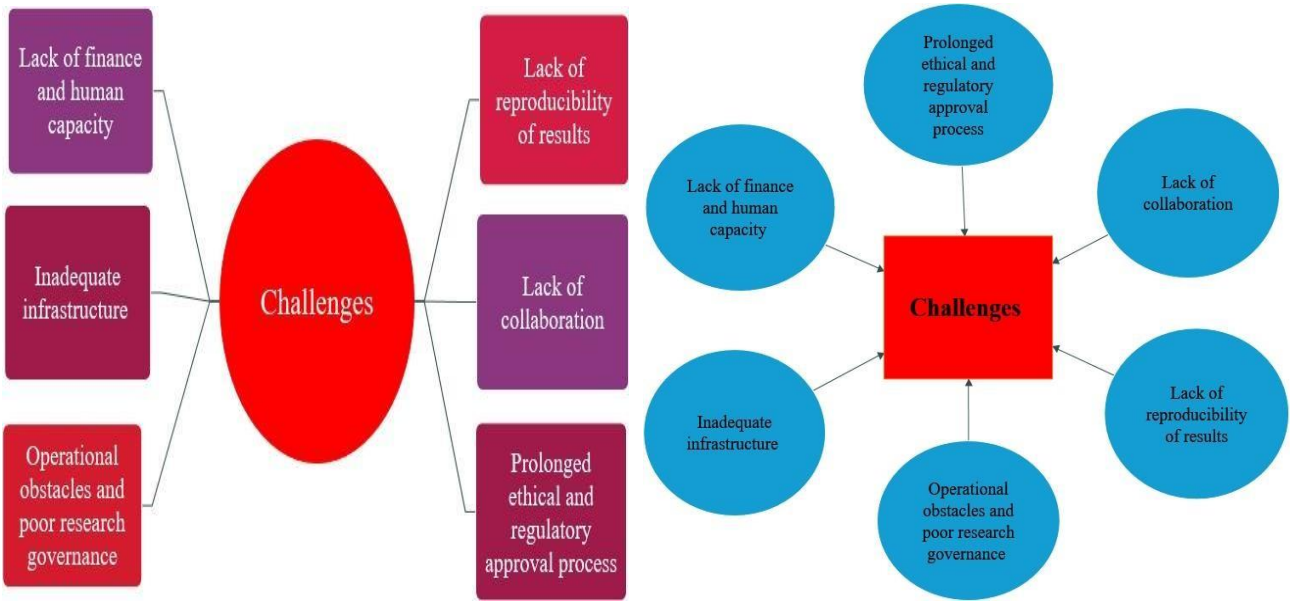
Name	Description	Files	References
Opportunities	Anchor codes or containers to represent sentences or phrases describing the existing opportunities for translating animal research into human trials. Alternatively, it is an anchor code for my second research question, which is "What do you thing about the possible enablers /opportunities for translating of animal research into human trials?"	0	0
Growing infrastructure and resources	This is the theme to represent for child nodes which are related to infrastructures like facilities, and resources including materials, populations	0	0
Availability of animal model	There might also be many opportunities including using of animal models following proper ethics	1	1
Available local product	Related to availability of plants used locally for treatment by the community	1	1
Availability of medicinal plants	Access to medicinal plants	1	1
Better facilities	Better facilities; laboratory facility and available experimental set ups, are now a days improved than in the previous years	5	7
Big number of institution in	Big number of institutions on basic sciences and if we give them	1	1

Step 6: Themes were generated to address the research questions and visual displays were done.

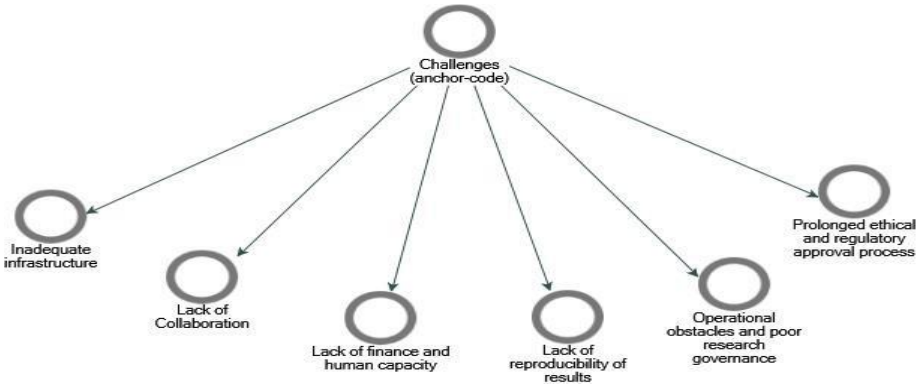
A. Hierarchy charts (tree –map and sunburst) compared by number of coding references



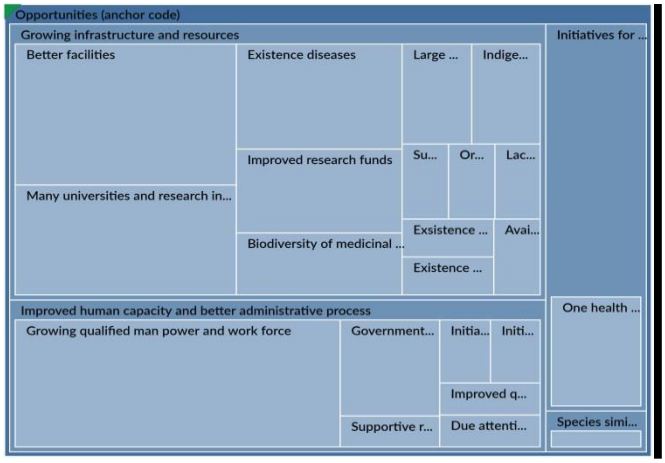
B. Mind-map, concept map (from left to right) for themes emerged as challenges

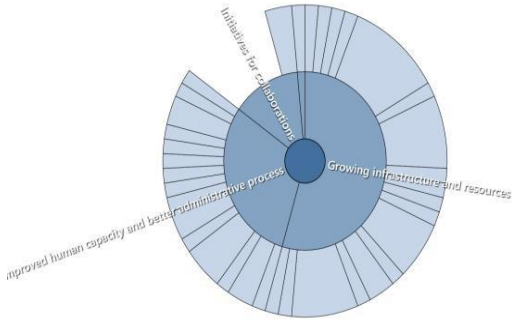


C. Project map for themes emerged as challenges

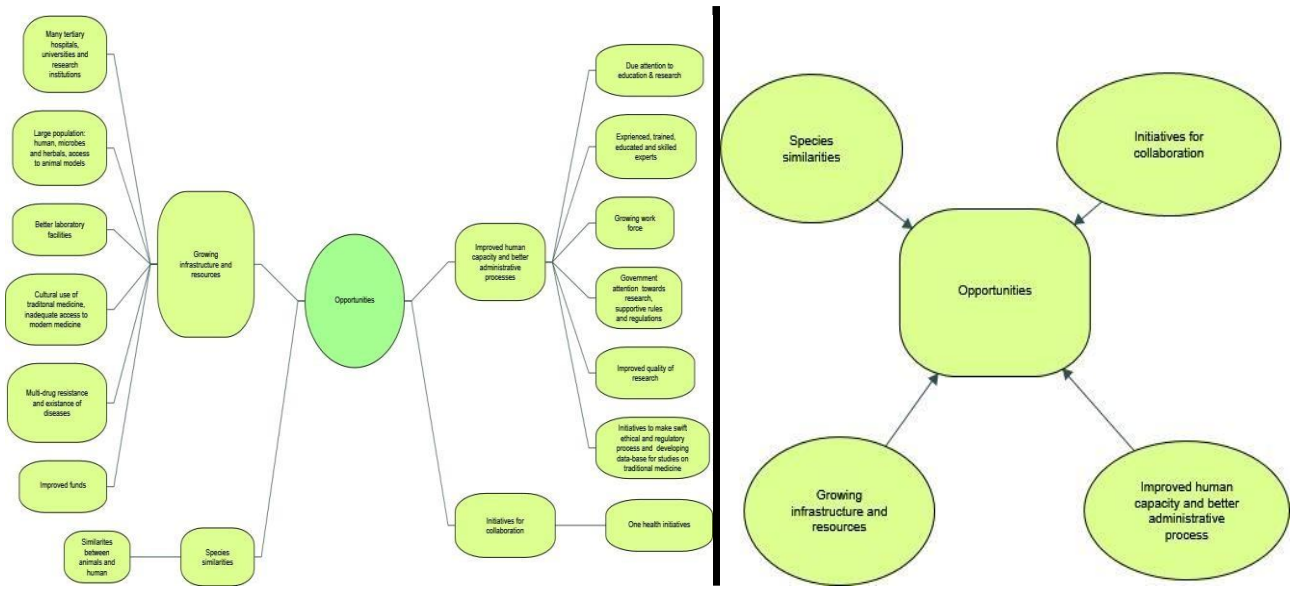


D. Hierarchy charts (tree –map and sunburst): themes emerged as opportunities compared by number of coding references

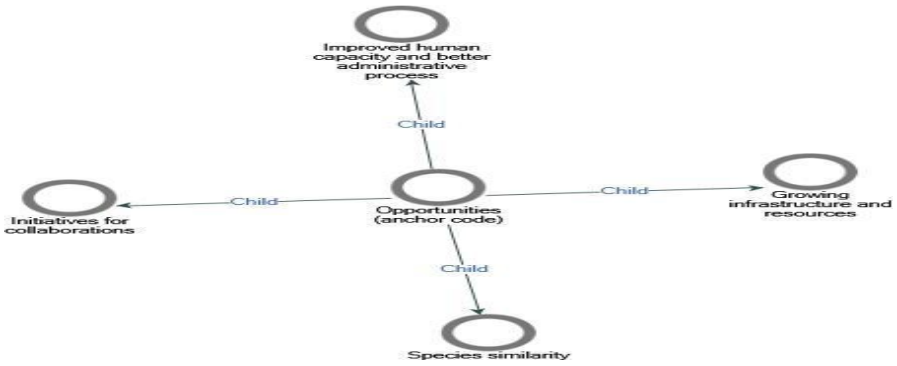




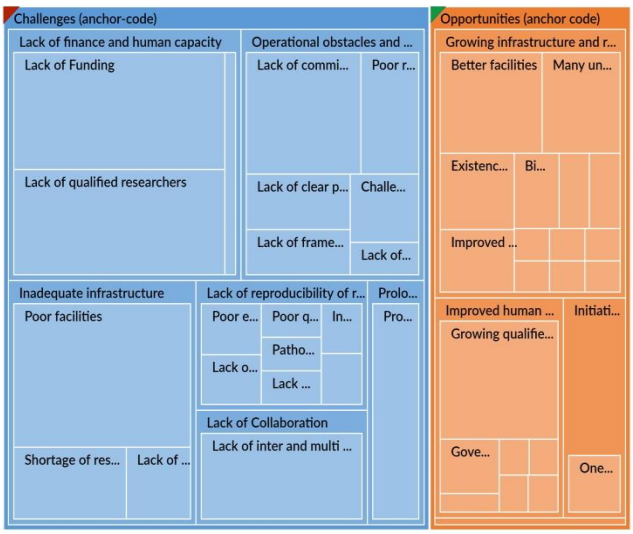
E. Mind map and concept map from left to right for themes (opportunities)

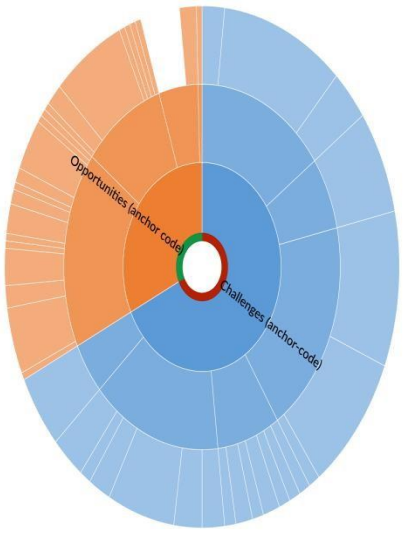


F. Project map for themes emerged as opportunities

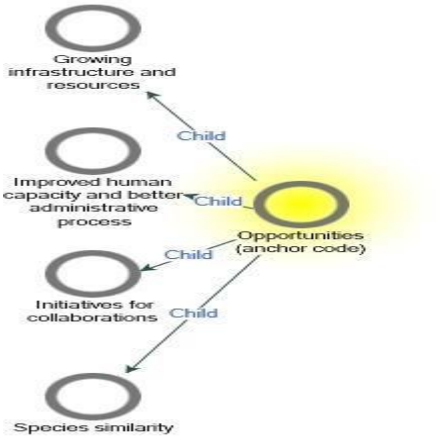


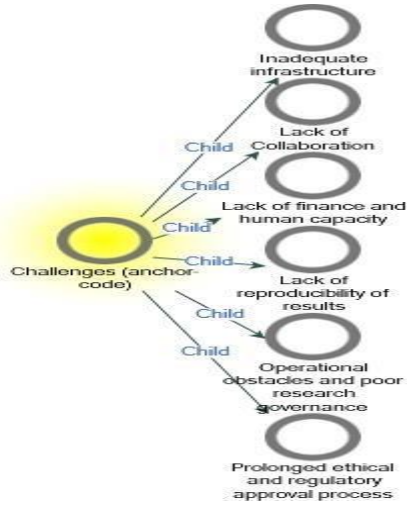
G. Hierarchy chart for themes emerged as challenges and opportunities compared by number of coding references using tree-map and sunburst





H. Comparison diagram between themes emerged as challenges and opportunities





11. DECLARATION

I, the undersigned, declare that this study is my original work in partial fulfillment of the requirement for the Degree of Masters in Clinical Trials and has not been presented for a degree in this or any other university. All source of materials used for this thesis work have been duly acknowledged.

Name of principal investigator: Askale Abrhaley (DVM, MSc candidate in Clinical Trials)

Signature: _____

Date: _____

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

This proposal has been submitted for approval to:

Advisor(s):

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   Signature: _____ Date: _____

Place: Addis Ababa University, Aklilu Lemma Institute of Pathology

2. Asrat Hailu (MSc, PhD, Professor)

   Signature: _____ Date: _____

Place: Addis Ababa University, College of Health Sciences