

**Barriers and enablers to locally-led clinical trial conduct in
Low and Middle Income Countries;
Strategies for developing locally sustainable health
research capacity**



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A thesis submitted in partial fulfilment of the requirements for
the degree of Doctor of Philosophy in Clinical Medicine
Michaelmas Term, 2014

Abstract

“All nations should be producers and users of research as well as consumers”

The 2013 World Health Report [1]

Many Low and Middle Income Countries (LAMICs) still lack sufficient health research capacity to build a local evidence-base with which to inform policy and improve population health. Recognising this, The 2013 World Health Report called for all nations to be producers of health research. To achieve this, new strategies that can develop sustainable locally-led capacity are required. Among the health research capacities needed, ability to conduct clinical trials is important. However, there is no evidence-informed guidance on the best ways to develop locally-led trial capacity. This thesis aims to fill this gap.

Three cases-studies using qualitative methods to explore the barriers and enablers to locally-led trial conduct were conducted in Ethiopia, Cameroon and Sri Lanka. Current and potential local trial researchers and health research system stakeholders were recruited. A synthesis of the health research capacity development literature was conducted to compare the case-studies' findings with wider published perspectives. These data permit an examination of the key issues facing the development of locally-led trial capacity in LAMICs.

Barriers and enablers to locally-led trial conduct were found at macro, institutional and individual levels. Although different country research systems, and institutions and individuals within them, were variably successful at conducting trials, the key issues and mechanisms influencing successful trial undertaking were largely similar. Agreement among the case-studies and with the diverse literature suggests that many of the findings will be transferable to other LAMICs, and are also of relevance to other health research methods.

A conceptual framework explaining the antecedents and consequences of locally-led trial undertaking in LAMICS is presented. This identifies the following factors as important for supporting locally-led trial undertaking: awareness and appreciation for health research and clinical trials; motivation to conduct clinical trials; availability of human resources with trial knowledge and technical skills; research leadership capabilities; ability to form collaborations, effective teams and acquire resources; trial management dedicated to sustainable capacity development and producing useful research; and system-wide prioritisation of health research. The theories of change presented within this framework are used to develop practical recommendations for development of locally-led trial capacity in LAMICs. These recommendations have four inter-related goals: fostering pro-research cultures in stakeholder institutions; developing trial leaders and staff; providing a facilitative operational environment for trials; and ensuring trial research has an impact. However, to create the will to enact change, advocacy from research champions and conducting trials in a way that benefits local institutions and population health is needed.

Acknowledgements

Firstly I would like to thank the Nuffield Department of Medicine for their generous scholarship, without which this DPhil would not have been possible.

Perhaps more important than the money, were my fantastic main supervisors: Dr (soon to be professor) Trudie Lang, with her ceaseless enthusiasm, support, and pragmatic guidance; and Dr Clare Chandler who schooled me in the world of social science, drove me to enquire more deeply, and was so patient in her teaching. Together you were the Ying and Yang of DPhil supervisors. Thank you also to my additional supervisor, Professor Brian Angus, for his calming wisdom.

I am also hugely grateful and indebted to my collaborators, Professor Fikre Enquselassie, Dr Julius Atashili and Professor Sisira Siribaddana, for making the fieldwork possible, productive and hugely enjoyable. Thank you also for your guidance and interpretations, to which I hope I have done justice.

My DPhil would also not have been nearly as rewarding or enjoyable without the wonderful Tropical Medicine and Global Health Network team. You made coming into work a pleasure and kept me relatively sane.

Finally, thank you to my wonderful family, particularly my wife Karla, for her support, love and patience through the barriers and enablers to DPhil conduct!

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List of abbreviations

- ❖ ADKAR – Awareness Desire Knowledge Ability Reinforcement
- ❖ EDCTP – European and Developing Countries Clinical Trial Partnership
- ❖ FGD – Focus Group Discussion
- ❖ FIT – Foreign Initiated Trial
- ❖ GCP- Good Clinical Practice
- ❖ GCLP – Good Clinical Laboratory Practice
- ❖ HIC – High Income Country
- ❖ HINARI – Access to Research in Health Programme
- ❖ HRCD – Health Research Capacity Development
- ❖ HRP – Special Programme of Research, Development and Research Training in Human Reproduction
- ❖ INT – Interview
- ❖ IRB –Institutional Review Board
- ❖ LAMIC – Low and Middle Income Country
- ❖ LIT – Locally Initiated Trial
- ❖ NHS – National Health Service (UK)
- ❖ NHRS – National Health Research System
- ❖ PM – Process Mapping
- ❖ PPT – Participant
- ❖ R&D – Research and development
- ❖ RBSE – Role Breadth Self-Efficacy
- ❖ SIDCER – Strategic Initiative for Developing Capacity in Ethical Review
- ❖ TDR - Special Programme for Research and Training in Tropical Diseases
- ❖ UN- United Nations
- ❖ WHO – World Health Organisation

PART I: INTRODUCTION

“Strengthening research capacity in developing countries is one of the most powerful, cost-effective, and sustainable means of advancing health and development” - 1990 Commission on Health Research for Development [2]

Chapter 1: Introduction and the research question

1.1 Structure of thesis

This thesis is organised into five parts.

- Introduction: *chapter one* will justify the research question and present the aims and objectives, and *chapter two* will present a systematic literature synthesis of health research capacity development.
- Methods: *chapter 3* will present the methods used in the empirical results chapters.
- Results: *chapters 4, 5 and 6* will present results from the three case-studies. The individual case-study findings will be discussed with reference to relevant theory, and the findings from each case-study will be iteratively compared to the previous ones to identify important reoccurring issues requiring greater consideration.

- Discussion: *chapter 7* will summarise and compare findings from the literature synthesis and results chapters. These findings will then be developed into a holistic model presenting the antecedents and consequences of trial undertaking. This model will then form the basis of recommendations to develop locally-led trial capacity. These recommendations will then be compared to other relevant capacity building models and the strengths and weaknesses of the overall findings will be discussed. Conclusions will then be presented.
- Appendices: contains the bibliography of references, case-study topic guides, and copies of publications and other outputs.

1.2 Justification for the research

1.2.1 The need for health research in LAMICS

Low and Middle Income Countries (LAMICs) disproportionately suffer the greatest burden of disease globally [2]. At the turn of the millennium LAMICs accounted for 85% of the world's population but 92% of the global disease burden [3]. To improve their health and development status, it was [2], and still is [1], recognised that more research is required into conditions that cause the greatest burden of disease in LAMICs.

It is widely accepted that this research needs to be conducted, as much as possible, within the countries that suffer the greatest burden of disease [4]. This proposal partly arises from ethical concerns over the potential risks and benefits for local stakeholders [5] but also because research evidence produced in one setting may not be directly applicable to other contexts [6]. This may be due to differences in disease profile, population genetics, environmental conditions, behavioural and cultural factors and resource availability [7 ,8]. Externally generated evidence is

often treated with caution by policymakers delaying its adoption into clinical practice and limiting its usefulness for policy and practice [9-11]. Therefore, in LAMICs, situated research is argued to be needed to “propose culturally apt and cost-effective individual and collective interventions, to investigate their implementation, and to explore the obstacles that prevent recommended strategies from being implemented” [7].

Problematically, back in 1990, it was found that less than 10% of global funding for health research was devoted to 90% of the world’s health problems [1 ,2], which is now known as the 10/90 gap [3]. This meant that LAMICs were seriously under-represented in terms of health research relative to their disease-burdens. This was mostly due to the poor state of their economies and rudimentary research capacity preventing national research conduct [8 ,12 ,13]. This led to The 1990 Commission on Health Research for Development stating that strengthening research capacity in LAMICs is “one of the most powerful, cost-effective, and sustainable means of advancing health and development” [2]. This marked the beginning of a “revolution” in health research [8] where there was a surge of investment and concerted effort to conduct health research aimed at solving health problems in LAMICs [3].

1.2.2 Progress in health research in LAMICs

This international attention to LAMIC health research is considered to have stimulated encouraging progress in terms of the volume and quality of research conducted in LAMICs [1][15][16]. Although causality cannot be assigned due to lack of monitoring data [14], this improvement is attributed to a variety of mechanisms, including foreign investment [8], a revised strategic focus at the international level [15], and international research collaborations and networks between High Income

Country (HIC) research organisations and LAMIC researchers [16-18]. HIC involvement in LAMIC health research [1 ,13 ,19] is deemed necessary to overcome local capacity constraints and stimulate research by providing their greater resources and expertise.

However, this growth has been uneven and significant evidence gaps persist [1]. Furthermore most of the research conducted in LAMICs was led by High Income Countries (HICs) [17 ,20], and despite some improvements, many LAMICs still lack capacity to self-sufficiently undertake research [1] and translate findings into policy [17 ,21]. As such, development of LAMIC nation's capacity to address their own health problems appears enduringly problematic, despite years of international collaborations and investment [1]. Therefore these gains in health research, in most circumstances, do not appear sustainable without continued strong foreign support [12 ,22], which is itself questionable in light of recent austerity reducing international development assistance [1 ,23].

Part of the blame for this is broadly attributed to LAMIC governments failing to take responsibility for national health research [12 ,22] and therefore not prioritising and investing in research, despite often growing economies [1 ,23]. This perpetuates inadequate local research capacity in terms of: stewardship and governance [4 ,10 ,24]; human [25-27] and material resources [25 ,28]; research support [12 ,28]; knowledge resources [26 ,28] and infrastructure [29]; and translation of research into policy and practice [25 ,30-32]. These capacity constraints then introduce barriers that inhibit research generation [10] and make local researchers dependent on foreign collaborations [33]. The *chapter 2 literature synthesis* explores these issues in greater detail.

HIC collaborations are also seen to be at fault for failing to develop local research capacity. This is because the Commission on Health Research for Development said that to advance cost-effective and sustainable health and development [2], *strengthening* research capacity was needed in addition to health research. However most HIC collaborations apparently failed to strengthen local capacity, and only concentrated on research.

Although complex and debated, the general reason for this was that HIC collaborations' prioritised research conduct over capacity development in order to speed up finding solutions to urgent health problems [8 ,34]. Accordingly they often bypassed local institutions by setting up parallel structures [5 ,35] and failed to adequately include local researchers and stakeholders in research conduct [5 ,35] which prevents the possibility of local capacity development [23 ,34 ,36 ,37]. Furthermore, foreign actors often set LAMIC researcher agendas with little local inclusion because projects were externally financed and led. These were argued to sometimes be wrongly targeted to be of use to local decision-makers [17]. Finally, this externally driven approach [24] where research was essentially done for or on LAMICs, rather than with or by them [38] was also argued to obstruct nation states' ability to assume responsibility for research [31 ,38]. This is because it took initiative and involvement away from local stakeholders [38]. These issues are addressed in more detail in the chapter 2 literature synthesis.

1.2.3 Locally-led research: A potentially better strategy for developing more self-sufficient research capacity.

To enable more self-sufficient research conduct, there have been calls for enhanced local ownership over national priority setting [17], greater engagement with local research communities [15], and research conducted in line with national health strategies [39]. Supporting locally-led research is seen as important for achieving this because it is argued to have several advantages over foreign-led research. Research topics developed by local investigators are argued to be more applicable to local population needs because they are developed using local healthcare knowledge [40] and are more likely to be driven by a national agenda [41]. This makes locally-led research more demand-driven and responsive to a country's needs, which makes their evidence more useful for policy [42]. Furthermore, because local researchers may have better relationships with local policy makers than foreign researchers [31], and can present research to policy makers with an understanding of the political and cultural context [43], they are more likely to be able to influence policy [40]. Importantly, when research is locally owned it also offers greater involvement for local staff and institutions [44] which facilitates skill development [45] and strengthening of institutional capacities [46].

Development of locally-led research capacity has received increasing attention and a number of suggestions, development frameworks and guides for “good” capacity development practice, in terms of development of locally-led research capacity, have been produced [14 ,31 ,40 ,45 ,47-49]. However, these suggestions have been presented since the millennium, and little appears to have changed given that HICs still dominate LAMIC research [44 ,50 ,51] and the 2013 World Health

Report recently reiterated that “all nations should be producers and users of research as well as consumers”, noting that this was not yet the case [1]. This suggests that if locally-led research capacity is to be developed, further consideration of how to develop local research capacity is required. Indeed, the 2013 World Health Report acknowledges that recommendations to develop local research capacity are not comprehensive [1].

1.2.4 The need for evidence-based and contextually-situated recommendations

Part of the problem with developing local capacity to conduct health research maybe that most of the current recommendations are too generic to be useful for a specific development intervention [47]. This is because experts suggest that for capacity development to be successful, tailoring of capacity development to the specific context [24 ,52] and goals of the development activity is needed [47]. To be able to choose the most appropriate interventions for a given context, information on the contexts where the recommendations came from [30], and the context where capacity development is to be delivered is needed [24 ,52]. Therefore, many of the current one-size-fits-all solutions that do not situate their recommendations within the contexts and types of research they are appropriate for, are unlikely to be helpful for developing a specific type of research capacity within a given context [28 ,31 ,53].

Part of the reason that many recommendations are generic is that there is little detailed and contextually embedded research on the status of national health research systems [24 ,52] or health research capacity development strategies [30]. This paucity of empirical evidence for informing development strategies was identified by both authors [54 ,55] and the *chapter 2 literature synthesis*. This is

problematic given the opinion that development recommendations should be based on situated empirical evidence [17 ,24 ,51 ,52]. This all suggests that to develop sustainable local research capacity, more situational analyses [24 ,52] and empirical research on the strengths and weaknesses of national health research systems [1] and how to develop them are needed [54 ,55]. Furthermore, recommendations based on this data need to be presented alongside the research that informed them, so that other enactors seeking to develop capacity in a different context can know if the recommendations will be appropriate for their aims. This will be particularly important where resources for capacity development are constrained, because it will allow selection of the most impactful and urgently-needed interventions.

1.2.5 A critical evidence gap: development of locally-led clinical trial capacity

One area in particular need of specific and situated evidence-based recommendations to develop sustainable and self-sufficient capacity is clinical trials.

Clinical trials are very important for providing evidence to inform health policy in LAMICs [8]. Although not always the most appropriate method, the reason that clinical trials can be so useful is that data arising from them is considered the highest quality or “gold standard” evidence [1 ,36 ,56]. As such they are considered very important for establishing the efficacy and safety of new interventions [36 ,56], informing systematic reviews that are increasingly promoted to guide clinical decision making around the world [1 ,6], and providing convincing evidence to influence public health policy [4 ,57 ,58]. Indeed, of the 12 case studies of research that have been useful for addressing research questions and informing policy pertaining to universal health coverage presented in the 2013 World Health Report, 5 were clinical trials, and one was a systematic review based on trial evidence [1].

It is worth noting that this thesis adopts the definition of clinical trial used by the World Health Organisation, which is “any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes...This definition includes Phase I to Phase IV trials.” [59]. As such, this definition encompasses randomised control trials on any health interventions, not just clinical topics in clinical settings. This definition is also used by the International Committee of Journal Editors and is applied to clinical trials requiring registration [60].

Given the need for more high-quality [8] context -specific data for local decision-making [61], more clinical trials in LAMICs addressing developing country health concerns have been called for by international research actors [1 ,3 ,9] and the LAMIC research community [37 ,41 ,62 ,63]. Like other types of health research, local ownership and leadership of these clinical trials is seen as important for developing self-sufficient trial capacity and enabling LAMICs to answer their own research problems sustainably. In recognition of this, in 2005 the World Health Organisation stated that the establishment of Africa-owned research centres capable of running their own clinical trials was an international priority [49]. However, like other types of health research, despite the increasing conduct of internationally-led clinical trials in LAMICs [9], development of self-sufficient trial capacity has proved elusive; clinical trial capacity remains limited [9 ,34 ,41 ,63 ,64], too few clinical trials are conducted [34 ,64], and most trials are still foreign-led [9 ,55]. These issues will be presented in further detail in the *chapter 2 literature synthesis*.

Indeed, the 2013 World Health Report suggests that clinical trials may actually be the most difficult research design to conduct in LAMICs because they are often

resource intensive, logistically and technically complex, and relatively slow compared to other experimental and observational methods. Therefore due to capacity constraints, research designs with less experimental rigour are often used to find a compromise between validity and resource capacity availability, regardless of whether they are the most appropriate method [1]. However, the World Health Report points out that the difficulty of clinical trials varies according to the intervention studied [1]. Disease management [36] and implementation trials [1 ,65] are likely to require less resources than novel therapeutic trials, and are therefore potentially more feasible for LAMICs to address self-sufficiently [1 ,36 ,41]. Furthermore, these topics are considered by many authors to be a neglected area because although they are needed to understand how existing interventions can be used more effectively [3 ,7 ,9 ,45 ,65], foreign-led trials usually only investigate novel interventions [23 ,41].

Despite the recognised importance of locally-led clinical trials for contributing towards more self-sufficient LAMIC health research capacity [9 ,36 ,41 ,55 ,63] and their comparative operational difficulty compared to other research methods [1], the chapter 2 literature synthesis and other authors [37 ,63] identify that very little literature explores how locally-led trial capacity can be developed. Rather the vast majority of clinical trial development literature is dedicated to developing LAMIC capacity to conduct international collaborative trials [17], rather than capacity to lead their own [37 ,63], and even this is sparse. Indeed, the chapter 2 literature synthesis only identified 3 papers in the health research capacity development literature that were dedicated to considering how locally-led trial capacity could be developed, and none of these were empirical. As such, development of local locally-led trial capacity has been largely ignored [62]. This is particularly problematic because although

locally-led trials are reported to face similar challenges as internationally-led studies [62], other authors suggest that they face unique challenges and will require special efforts to develop their capacity above and beyond those required to scale up foreign-led research [63 ,66 ,67].

As established above, the development of sustainable local research capacity requires situated recommendations informed by context-specific empirical research with a focus on specific development aims. Therefore the lack of these recommendations and any empirical research into the barriers and enablers to locally-led trial conduct is a critical block to development of locally-led trial capacity. Given the recognised importance of locally-led clinical trials, addressing this evidence gap is an important and urgent priority.

1.3 Research question: aims and objectives

Based on the above justification, it was decided that better understanding how to develop locally-led trial capacity in LAMICs would be an important, appropriate and potentially useful topic for a DPhil to explore. Recognition of this led to the following research question, aims and objectives:

Research question:

What are the barriers and enablers to locally-led clinical trial conduct in Low and Middle Income Countries and what are the best strategies for facilitating their conduct?

Aim:

The aim of this study is to produce reliable and robust evidence-based recommendations for the facilitation of locally-led clinical trials in Low and Middle Income Countries.

Objectives:

1. To identify, understand, and explain the barriers and enablers to clinical trial conduct in specific LAMIC contexts, with particular emphasis on locally-led trials
2. To compare and contrast findings from different research contexts to ascertain if any context-specific findings are transferable to similar research contexts, or more broadly generalizable
3. To develop a conceptual framework for the development of locally-led trial capacity in LAMICs, identifying which elements are context-specific, transferable to similar settings, or more broadly generalizable
4. To use the conceptual framework to formulate situated recommendations for the development of locally-led trial capacity in LAMICs, and to consider if these recommendations are also relevant to developing other types locally-led health research capacity in LAMICs

Chapter 2: Learning from the literature: A systematic review of health research capacity development in Low and Middle Income countries since the millennium

Health research capacity development is “a risky, messy business, with unpredictable and unquantifiable outcomes, uncertain methodologies, contested objectives, many unintended consequences, little credit to its champions and long-time lags” – Department for International Development, 2010 [46]

2.1 Introduction

A detailed systematic literature synthesis is required to provide a thorough understanding of the clinical trial capacity development field. It is also needed to be able to compare and contrast this thesis's findings with other author's opinions, recommendations and evidence from various research contexts. In doing this, novelty, transferability or generalizability of the thesis findings may be identified. However, the literature on locally-led trial capacity development, and even general clinical trial capacity development in LAMICs is so sparse that the scope of the literature synthesis had to be broadened to include literature concerning all health research capacity development (HRCD) in LAMICs.

At a time when the future of the Millennium Development Goals is being debated [1], it seems appropriate to review HRCD efforts post the year-2000. This body of literature on health research capacity development (HRCD) is widely regarded as

large and diverse with various complementary and contradictory understandings [68] and conceptualisations [1]. Therefore a systematic synthesis of this literature will not only be useful for this thesis but will also help clarify this confusing field by providing a unifying picture to appraise previous HRCD efforts, identify research gaps, and to learn what works, what doesn't and in what circumstances. Since capacity development is now something that most research actors are expected to participate in [8 ,33], or at least be knowledgeable on, this should prove useful to all stakeholders interested in learning how to undertake the complex business of HRCD, and will be of particular interest to actors working to develop locally-led, sustainable research capacity in LAMICs.

The objectives for this literature synthesis have 3 parts:

1. To map the field of HRCD and clarify the key streams of thinking
 - a. Identify and clarify the key definitions and terminology in HRCD
 - b. Identify and organise the key actors involved in HRCD
 - c. Identify and organise the voices participating in the HRCD discussion
 - d. To present clearly the main streams of thinking in HRCD
2. To summarise and critique the published literature to identify the most appropriate actions required to develop locally-led clinical trial capacity
 - a. To categorise and summarise the main approaches to HRCD
 - b. Summarise the main reported barriers to HRCD
 - c. Summarise and structure the main reported enablers to HRCD
 - d. To offer preliminary recommendations for future HRCD efforts aiming to develop locally-led research capacity in LAMICs, specifically locally-led clinical trials

3. To assess if the results chapter findings on locally-led trials have transferability or generalizability to other LAMIC research contexts or types of health research, or are novel. This third objective will be addressed in the final discussion chapter, once the empirical results have been presented.

2.2 Methods

This review considers the perspectives of all actors involved in health research capacity development that publish within academic and grey literature from 2000 onwards. Since the majority of this literature is qualitative, a qualitative review methodology was necessitated. The method used largely followed the meta-narrative methodology developed by Greenhalgh *et al* [69]. This method was developed to review diffusion of innovations in service organisations [70], in response to specific challenges with synthesising literature in their chosen topic (see box 2.1). Since the development of the meta-narrative method, it has become a widely recognised method for qualitative syntheses that face similar challenges [71]. A synthesis on the topic of HRCD literature shares these challenges; therefore I chose to follow the meta-narrative approach in this review. The 6 stages of the meta-narrative method are summarised in table 2.1 and explained in detail below.

Box 2-1 Challenges that prompted the development of the Meta-narrative method [70]

1. Large diverse body of literature from different disciplines with different conceptualisations of the phenomenon being studied
2. A lack of clear and consistent definitions, approaches and common understanding
3. Inconsistent study design
4. No established norms of quality or repositories to search
5. The need to avoid a narrow approach or superficial understanding

Table 2-1 The 6 stages of the meta-narrative method [69]

Planning phase	Outlining and agreeing on initial research question
Search Phase	"Browsing", identify seminal papers, searching databases
Mapping phase	Identifying key concepts, actors and definitions
Appraisal phase	Evaluating primary studies for validity relevance and collate results grouping comparable studies
Synthesis phase	Identify key dimensions of phenomenon, develop narratives, discuss competing findings in detail
Recommendations	Summarise overall messages within current contexts, distil recommendations for practice, policy and further research

2.2.1 Planning and search phase

After consulting with an Oxford University Library Services systematic review expert (Ms Nia Roberts), PubMed was deemed the most appropriate database to search. The justification for this was that PubMed would contain the most relevant articles for the purposes of the review; a preliminary search of PubMed confirmed this. The final PubMed search criteria (box 2.2) were a result of iterative experimentation, seeking a compromise between capturing relevant studies and preventing an unnecessarily large search result.

Box 2-2 Search terms used in PubMed

```
((((((((((((((capacity building[MeSH Terms]) OR (("developing"[Title/Abstract]) OR
"develop"[Title/Abstract]) OR "capacity"[Title/Abstract]))) OR
"strengthen"[Title/Abstract]) OR "strengthening"[Title/Abstract])) AND (((developing
country[MeSH Terms]) OR Africa) OR Asia) OR Latin America))) AND (((("trial"[Title]) OR
"trials"[Title]) OR "research"[Title]))) NOT clinical trial[Publication Type]) NOT informed
consent[MeSH Terms]) NOT waste management[MeSH Terms]) NOT air pollution[MeSH
Terms]) NOT agriculture[MeSH Terms]) NOT ("Na6(H2O)8(ZnAsO4)6" [Supplementary
Concept] OR "K3Zn4O(AsO4)3" [Supplementary Concept])
```

The final PubMed search was run on the 20/06/13 and yielded 1668 papers. The titles and abstracts of these papers were then scanned for eligibility. After preliminary screening it became clear that much of the literature pre 2000 was not relevant to the current day situation. This was because of the paradigm shifts in global health at the turn of the millennium [3 ,8] (see page 31 of the literature synthesis for a history of capacity development). Many papers post 2000 also effectively reiterated previous important themes and included historical summaries. Therefore it was decided to discard all papers pre-2000. The criteria used to evaluate eligibility are shown in box 2.3. Non-English language publications were excluded due to no resources being available for translation.

Box 2-3 Eligibility criteria for assessing papers

Inclusion – Papers that:	
• Broadly address health research capacity development • Specifically address components of health research capacity development e.g. enablers to health research training provision	
Exclusion – Papers that	
• Call for capacity development but have no consideration of purpose, implementation and no further relevant discussion e.g. unrelated papers that conclude with “further capacity development is needed”. • Include specific components that could be considered research capacity development, but are not presented in any capacity development context e.g. discussion of disease priorities with no reference to benefit or need for capacity • Healthcare delivery when research not considered • Occupational health research • Do not have English language abstract • Published before year-2000	

Much of the capacity development literature is considered “grey literature” and does not appear in PubMed searches. Therefore a hand search of Google and Google Scholar was performed using the terms “Health AND research AND capacity AND strengthening OR Building OR Development”. All literature added

from Google were found in the first 10 pages. After the first 10 pages, no search results were relevant to the study. Literature collections of the authors and other experts were also hand searched and references snowballed. Individual journals were not hand searched due to time constraints.

This process yielded 292 papers. After, reading these papers in full, a further 52 papers were discarded because they did not meet the inclusion criteria upon closer inspection. Therefore, two-hundred and forty papers were included in the final analysis. The process of selection and breakdown of sources is shown in figure 2.1.

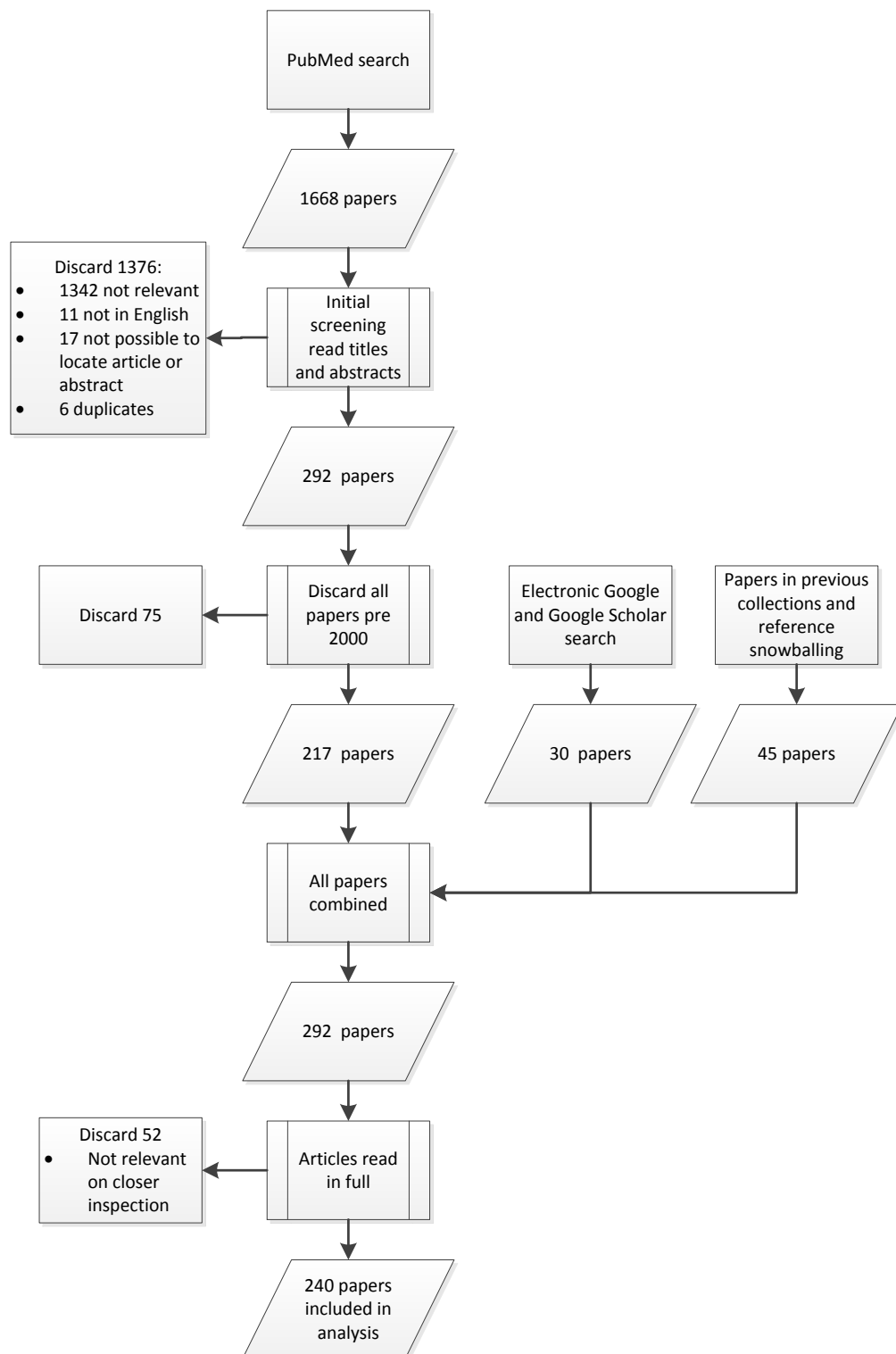


Figure 2-1 Process of selection and breakdown of sources

2.2.2 Mapping phase

The multitude and diversity of development actors means that knowledge on actor activities is fragmented and multiple conflicting terminology exists [31]. Therefore the sources required further organisation before analysis was possible. To achieve this, a table of definitions and typology of development actors was developed. A brief history of capacity development pre-2000 was also assembled to contextualise more modern contributions.

To ensure that the source content was interpreted within the context of its attributes, even when broken into themes and narratives, a tagging system was used instead of a traditional extraction form. All sources were organised in EndNote X7 (Thomson Reuters) and associated citations, metadata and PDF copies of the documents were attached. These data were then imported into Nvivo 9 qualitative analysis software (QSR International) where the sources were given tags using deductive codes for key attributes. The main data items collected and attached to sources are shown in table 2.2. Coding was complete by Samuel Franzen only. Although it would have been desirable to have a second coder with whom to discuss the coding framework, and thereby question my interpretations and further develop the coding framework and analysis, this was not possible due to resource constraints. The limitations of this are discussed further in section 2.2.4 (page 24).

Table 2-2 Main data items (meta-data and attributes) collected for sources

Data item	Method of collection and tagging
Document type (journal article, government document etc.)	EndNote metadata
Author	EndNote metadata
Author department	EndNote metadata
Author address	EndNote metadata
Year	EndNote metadata
Publisher	EndNote metadata
Date of issue	EndNote metadata
Access date	EndNote metadata
Abstract	EndNote metadata
File attachment	EndNote metadata
First author institution type	Nvivo Deductive coding
Location of first author institution	Nvivo Deductive coding
Region of capacity development	Nvivo Deductive coding
Main topic of capacity development interest	Nvivo Deductive coding
Main disease of interest	Nvivo Deductive coding
Are clinical trials a key discussion point	Nvivo Deductive coding
Basis for viewpoint e.g. opinion, empirical, experience etc.	Nvivo Deductive coding

2.2.3 Appraisal, synthesis and recommendations phase

Since the majority of sources in this synthesis lacked any empirical base or explicit design, the appraisal of quality was not possible. Furthermore, all stakeholders' views, regardless of the perceived validity of their viewpoint, were considered important. Therefore, similarity of arguments within the literature was used as an indicator of current agreement on a topic or popularity of an idea, rather than using indicators of quality to judge contribution to the field. To synthesise the diverse HRCD literature, the contributions need to be framed within a "storyline" that recognises where the contribution came from. *Greenhalgh et al.*'s method explicitly catalogues these storylines as "meta-narratives" [69]. Developing meta-narratives

provides context to contributions whose underlying assumptions and interests would otherwise be opaque. Although less prescribed than a quantitative systematic review, this approach pragmatically allows a plurality of ideas, recognising there may be no single correct answer.

Where several *authors in the literature* connected themes similarly in their papers, these themes were grouped *by the reviewer* into meta-narratives. This analytical process is similar to that used in thematic coding analysis, where *reoccurring themes* that are conceptually related are grouped into *concepts*. Once the meta-narratives had been finalised they were systematically applied to all the papers. No prior theory beyond the guidance presented by Greenhalgh *et al.* [69] was explicitly used to help identify and categorise the meta-narratives. Instead, iterative rounds of open data-driven inductive coding were used.

Although the meta-narratives that were inductively identified were useful for uncovering the main streams of thinking, they were not successful in grouping capacity development mechanisms or barriers and enablers to research. This was because most contributions on these issues were isolated, uncomprehensive, and did not consider drivers or solutions. Therefore it was decided that these issues should be conceptually grouped according to *the reviewer's* deductive conceptual groupings. In this case, prior theory on system-based approaches to capacity building and the main modalities of health research system strengthening were used to organise and present the findings. As such this approach is closer to summative thematic analyses such as framework approaches.

After the synthesis was completed, the findings were written and recommendations made where possible.

2.2.4 Limitations and risk of bias in the meta-narrative synthesis

PubMed was the only database used, so some articles may have been missed. However, the meta-narrative method aims to develop overarching narratives through saturation of themes, rather than include every eligible article, so using additional databases would add little to the study. Using PubMed as the primary database also means that contributions will be skewed towards an academic publication bias. Hand-searching, expert recommendation, Google and Google Scholar were used to help overcome this, but the lack of formal indexing for grey literature means that some non-academic contributions will be missed. However it is expected that most seminal papers have been identified.

Capacity development discussion is highly political and much is based on personal opinion informed by theoretical or ethical standpoint. Accordingly much of it is biased. Rather than attempt to remove the bias it was explicitly studied to highlight authors' implicit conceptual frameworks, so that readers can make their own informed opinion.

There is also inherent reviewer subjectivity in the meta-narrative method because this is an interpretative exercise. Recognition of this acknowledges that all such findings are inevitably influenced by the reviewer's own perspectives and values. Having a second coder would have been helpful to discuss interpretations and develop the analysis. However, the epistemology of interpretative approaches is at odds with the concept of improving validity through inter-coder reliability comparisons, since regardless of the number of coders working on the analysis, the emerging coding scheme could never be seen as 'the objective truth', given that there are numerous perspectives that could shape interpretation. Ensuring quality

of interpretation relies, rather, on being transparent in offering explanations of meanings rather than presenting definitive causations, and explicitly acknowledging the subjective nature of the analysis and the bias this creates. While no published protocol exists for this review and it was not prospectively registered, all the search terms and methodological process have been made transparent so that others can understand how the study and analysis was conducted, and replicate this study, if desired, even if other equally valid conclusions might be drawn out.

2.3 Background information

2.3.1 Definitions

As stated previously, the concept of capacity development has multiple conflicting definitions and can be confusing if poorly defined [68]. Health research development is no exception and in some cases no widely accepted definitions exist. Therefore, the first stage in the review process was to come to grips with the key terminology and develop a typology of relevant working definitions so that all readers have a common understanding.

The main terms used in the literature to describe the process of increasing capacity are: Capacity Building, Capacity Strengthening and Capacity Development. Although these are often used interchangeably, 'capacity building' is taken to mean an intention to establish de-novo capacity such as research infrastructure, whereas 'capacity strengthening' emphasises the enhancement of pre-existing capacities which themselves influence outcomes and activities [72]. For the purpose of this synthesis, we will consistently adopt the terminology of capacity development. Although this has some pejorative connotations (assumption that

there is little extant capacity as with “capacity building”), in its broadest sense capacity development could involve both building capacity and strengthening. It also semantically links capacity development to the international development agenda. Therefore, for the purposes of this study, it is the most encompassing term to describe broadly the process of increasing capacity. Other key terminology used in this thesis and reasons for adopting these definitions are described in table 2.3.

2.3.2 Actors

Table 2.4 shows the actor typology developed for the literature synthesis. This categorises the study population into groups of actors according to their development activities. This is the most complete and detailed typology of HRCD actors found in the reviewed literature.

Table 2-3 Key terminology and definitions used in this synthesis

Term	Definition adopted	Examples	Comments and caveats
Health research	“Health research is the systematic generation of new knowledge in the field of medical, natural, social, economic and behavioural sciences and its use to improve the health of individuals or groups”. [8]	<i>A main purpose is to produce the information and knowledge for identifying the challenges to the health system and to provide solutions. We acknowledge that other drivers such as commercial interests and economic and political motivations may also be important. However, for the purpose of this study, the implicit goal is to benefit individual or population health.</i>	Encompasses research labelled Global Health Research, Tropical Medicine, International Health, Population Research. Also encompasses “Clinical research”, although this may be considered by some as more narrow than “health research”, dealing with research only in clinical environments. However, for the purposes of this thesis, making this definition will be confusing since it suggests that clinical trials are restricted to clinical environments.
Health research capacity development (HRCDD)	“Capacity development is defined as the ability of individuals, organisations or systems to perform appropriate functions effectively, efficiently and in a sustainable manner. When applied to health research, this translates to enabling both individuals and institutions to define health problems, set objectives and priorities, build sustainable institutions and organisations and identify solutions to key national health problems”. [73]	Conducted by a large numbers of actors including: private foundations, multi and bi-lateral funders, international organisations, consortia, research councils, universities, NGOs and Industry. Examples include Rockefeller Foundation, The Swedish International Development Agency and WHO TDR. Usually involves knowledge or resource transfer at individual, institutional or macro levels.	This definition by Magwaza et al. [73] was found to be the most straightforward and encompassing definition of health research capacity development
Clinical trial	“A clinical trial is any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes...This definition includes Phase I to Phase IV trials.” [59]	Interventions include but are not restricted to drugs, cells and other biological products, surgical procedures, radiologic procedures, devices, behavioural treatments, process-of-care changes, preventive care, etc. [59]	This definition is taken from the WHO Trial Registry Platform [59]. Clinical trials may also be referred to as interventional trials, randomised control trials or simply trials.
Locally-initiated clinical trial (LIT)	Clinical trials that have been conceived, designed and led by an individual principal investigator or team of collaborating investigators and where the research is conducted in their home LAMIC country i.e. Local research. The LIT could have a foreign collaboratory input and foreign sponsorship or funding, but to be considered an LIT the local investigator(s) must be the leader(s) of the study and maintain overall ownership	A clinical trial conducted in a LAMIC country where the nationally-based researcher initiates the research, is custodian of the protocol and lead authors on publications.	May have foreign funding or international collaborators, as long as the local investigator maintains leadership and ownership. May also be called locally-led trials, or investigator-initiated or investigator driven trials, but only when the research is conducted in their home country.
Foreign-initiated clinical trial (FIT)	Clinical trials conducted in a LAMIC country but the main initiative, leadership or ownership comes from investigators outside of the country of recruitment.	A clinical trial conceived and designed by an investigator based at a university in the U.K. and carried out in a LAMIC country, with or without local collaboration.	May also be called foreign-led trials. These trials may have a local collaborator, but cannot be considered locally-led trials because the study conception, design and leadership come from investigators based abroad.

Research system	Concept representing a system designed to coordinate and manage health research at all stages of the knowledge cycle with the goal of improving health and health equity. The research system can be conceptualised as the environment or ecosystem that research takes place in [74].	Research systems encompass health research structures, regulations, governance, ethics, infrastructure, priority setting, financial and resource planning, acquisition and allocation at national, regional or global levels [75]. They include and connect all other levels, including the supra-national level.	Research system is not to be confused with “System Level”. “System Level” is often used to describe what we consider to be the “Macro Level”.
Supra-national level capacity	The term “supranational level” is used to convey capacity that is designed to intervene at and between internationally connected groups and nations.	Interventions include harmonisation of funding agendas, international funding databases, creation of international networks and consortia and increasing capacities of global governance groups.	This level is often subsumed within the term “system level”. However, it is important to distinguish between interventions at supra-national and macro levels.
Macro level capacity	The highest level of the national research system. Capacities at this level may be agenda setting, policies, national budgetary allocations, demand creation and strategic planning [10].	Government ministries such as Ministry of Health, Research or Education. Also includes regulatory and ethics bodies, funding bodies, top level administrative structures, professional associations and national registries.	Often used interchangeably with “System Level” [10]. However it is confusing because the system encompasses individual, institutional, macro and supra-national levels.
Institutional level capacity	Refers to the ability of institutions to fund, manage and sustain themselves to perform all tasks required to deliver their services or goals. Common institutions include: universities, hospitals, and ministerial departments.	Elements of institutions include: human resources, material resources (computers and machinery), infrastructure (libraries and laboratories), service connections (internet, water, and power), service delivery and finance and management systems.	Based on the working definitions used by The Global Forum for Health Research and the World Health Organisation as they encompass the most common conceptualisations of the term [3 ,10 ,24 ,74].
Organisational level capacity	The capacities of individual units within and governed by “institutions”.	Usually include departments or research units within universities or research divisions within ministries of health	The term “institution” is often used interchangeably with “organisation”. However, differentiating between these terms is useful because it distinguishes between the wider governing institution and organisational units within institutions [47].
Individual level capacity	Individual capacity development attempts to increase the capacities of individuals to perform their work effectively	Traditionally focused on producers of research. More recently extended to other stakeholders and includes “soft” skills training such as leadership.	Based on commonly accepted definitions used by The Global Forum for Health Research and the World Health Organisation [3 ,10 ,24 ,74].
Modality	Modality refers to the methods or organisational setup used to deliver development interventions	May include basket funding to institutions, vertical support to projects, or horizontal capacity development, collaboration or partnerships [17].	Similar to research model. Modality is distinct from “strategy” which also encompasses the intervention level and stage of knowledge cycle.
Stage of knowledge cycle	Stages of the knowledge cycle refers to the point of the research process the capacity development is targeted.	Stages include: knowledge generation, knowledge dissemination and communication, knowledge uptake to policies and priorities and knowledge demand creation [17].	A useful distinguishing term.

Table 2-4 Typology of actors in health research capacity development

Actor category	Examples of actors	Summary of typical HRCS activities				Example Sources
		History	Content	Level and mode	Stage in knowledge cycle	
Private Foundations or Charity Funders	Wellcome Trust, Gates Foundation, Rockefeller Foundation	Relatively new to the field of HRCS but increasingly important. Rockefeller Foundation has been involved since mid-1970s.	Thematically focused	Mostly individual development or specific projects often channelled through multi-donor research networks or consortia. Little investment in local institutions. Often prefer PPPS.	Mostly support knowledge generation but very recent moves to knowledge management and utilisation	[10 ,17 ,76 ,77]
Multi-lateral Funders- usually with stewardship roles	World Health Organisation, World Bank, African Development Bank, Global Fund	WHO is one of the oldest actors in HRCS through its Special Programmes for Research and Training. Most actors are well established organisations but relatively new to HRCS.	Have "world health governance" roles as well as prioritisation and funding. Often support thematically focused health research projects.	Usually channel funds through independent or subsidiary organisations. WHO provides individual development. Traditionally did not support institutions and had little system interest. However, now taking the lead in system approaches and may channel funds through local institutions. Provide advice and voluntary-compliance governance. Strong advocacy and agenda setting roles.	Typically support knowledge translation activities but increasing emphasis on research dissemination, utilisation and knowledge management	[17 ,78]
Bilateral Funders- usually High Income Country Governmental	Swedish International Development Agency, Department for International Development	Generally the longest running financial supporters of HRCS. Earliest in 1970's. However some are newer additions.	Varied	Usually support individual and institutional development. Little system development until very recently	Historical focus on knowledge generation but progressively more emphasis on knowledge utilisation and dissemination	[17 ,76]
Global Organisations with stewardship or funding brokerage roles	WHO TDR & HRP, Global Forum for Health Research, European and Developing Countries Clinical Trial Partnership	WHO TDR & HRP are some of the oldest actors in HRCS. Others are newer from mid 1990s. Often formed by, or as, a subsidiary of multi-laterals.	Stewardship roles set and promote global agendas. Also have multi-lateral funding brokerage roles.	Act as a catalyst to support and direct diverse actors to common goals. Usually fund and work with networks and consortia. Organise forums. Historically supported individual and institutional development but now support HRCD at most levels and modes. Provide advice and strong advocacy roles.	Originally interested in knowledge generation & translation but now tackle all stages of knowledge cycle	[3 ,8 ,13 ,76 ,79]

Consortia and Networks - may be subsidiary to Global Organisations	Alliance for Health Policy and Systems Research, International Network for Clinical Epidemiology, Central African Network on TB HIV/AIDS & Malaria	Largely a recent phenomenon forming mid-late 1990s onwards	Thematic based on disease of study, discipline or stage in knowledge cycle. Some advocacy or funding brokerage roles. Global, regional or local reach.	Individual and institutional support for specific projects or organisations. Not traditionally institution-wide or system development but recently more attention to those areas. Mixture of horizontal and vertical initiatives.	Collectively they cover the entire knowledge cycle; knowledge generation, Knowledge dissemination, knowledge utilisation, advocacy and communication	[8 ,76 ,80]
Public Private Partnerships and Product Development Partnerships	Medicines for Malaria Venture, International AIDS Vaccine Initiative, Global Alliance for TB Drug Development	Largely a recent phenomenon forming mid-late 1990s onwards. Over 70 formed between 1995 and 2003.	Thematically based on disease or intervention of interest. Product development "upstream" R&D research.	Development approaches usually concentrated on building capacity to run specific studies through vertical interventions. Recently a little more attention to more general individual level and infrastructure development.	Knowledge generation and strong emphasis on translation	[8 ,81]
LAMIC Funders, Research Councils and Institutes of Health	South African Medical Research Council, The National Research Council of Sri Lanka	Much less common than in HICs but increasing and some well-established.	Varies widely but usually in accordance with EHNR priorities and focus on specific conditions or projects. Reach usually national only.	Funding available is often limited but appears to be increasing. Formation of research sites, particularly centres of excellence. Individual and institutional development. Often in collaboration with international networks. early moves towards system development. May also carry out own research.	Mostly knowledge generation	[16 ,82]
LAMIC Governmental	South Africa, Brazil, Zambia	Highly variable often according to GDP but also economic policies. Some investing a lot, others not at all. Typically only recent investments in HRCD.	Variable but usually in accordance with ENHR priorities if present. May be linked to infrastructure development. Reach usually national only.	Some ministries have their own research centres and develop capacity "in house". Others provide project grants or individual development. Governments may upgrade or create research institutions. Investment value typically small due to resource constraints or low priority of research. However, some countries investing heavily. More recent attention to macro level capacities.	Varied. Knowledge generation common but recently agenda setting, stewardship, demand creation and knowledge utilisation increasingly important.	[31 ,72 ,75 ,83]

LAMIC Academic and Healthcare Institutions	University of KwaZulu-Natal, Makerere University, Fundação Oswaldo Cruz	Varied history. Some very well established in research but most new to HRCD. May be public or private.	Variable. Research may be in accordance with EHNR priorities, but may also follow global or regional priorities or investigator interest. Typically lower technology and investment than HIC research.	Mainly undergraduate and some graduate training. Provide institutional resources for research. Development of institutions usually reliant on governmental funds, unless private. Normally training and education takes precedence over research.	Knowledge generation	[35 ,84 ,85]
HIC Research Councils and Institutes of Health	Medical Research Council (UK), NIH (USA), Canadian Institutes for Health Research, Royal Society	Institutions with a long history but only recently (around 2000) expanding their role in HRCS	Varied. But no specific remit to conduct capacity development.	Provide various funding and scholarships for individuals to undertake post graduate training. Also fund specific research projects which may include institutional development. Normally work in collaboration with institutions from donor country. Usually not system level. Some encourage scientific excellence by forming links with other LAMIC societies, but do not conduct HRCD directly.	May directly conduct knowledge translation research e.g. trials themselves. Mostly support knowledge generation but may have smaller efforts in knowledge utilisation.	[10 ,86]
HIC Academic and Healthcare Institutions	University of Oxford, Institut Pasteur, Johns Hopkins University	A long history of research in LAMIC. Some project specific HRCD but only recently taking on more explicit capacity development.	Project focused around research goals. Varied topics often at the choice of researcher or funder agendas. May also follow ENHR. Normally higher budgets than LAMIC academic research.	Development is usually to facilitate a specific project. May involve developing research sites and staff. Often focus on centres of excellence. Individual development either in-country or at HIC universities. System development not common. Normally in partnership with local groups which increases knowledge transfer.	Mostly knowledge generation. Specific projects may target knowledge utilisation and sometimes dissemination but much rarer.	[35]
Industry	GlaxoSmithKline, IBM , Local industries	Pharmaceutical companies important but IT companies increasingly involved. International and national industry involved.	Product development and innovation technologies. Mostly in Asia. Currently less reach to Africa.	Develop capacity through technology or "know how" transfer. Infrastructure strengthening, particularly IT. May fund individual training or institutional development. Other actions include: not charging for services, free drugs, cash donations, royalty free licences and volunteering expertise. Usually work in partnership with other actors.	Knowledge generation and translation but also knowledge management. May work in other areas depending on company.	[86]

Non-Governmental Organisations (NGO)	Medicine Sans Frontiers, Drugs for Neglected Diseases Initiative, One World Health, local NGOS	Recent involvement in research and HRCD (post 2005)	Pragmatic output orientated. Either highly applied or product development R&D. Some work in partnerships with other actors.	Strengthen research within networks or embedded in health delivery. Usually individual or specialised institutional support. As part of civil society, have strong advocacy and moderation roles. Can mobilise resources towards non-profit activities	All stages of knowledge cycle.	[87-89]
Academic journals	International Committee of Medical Journal Editors, Lancet, PLoS, Tanzanian Journal of Health Research	Long history of discussion on HRCD but becoming increasingly prominent in last 5 years.	Advocacy and opinion leaders. Role as moderators and amplifiers. Provide access to information and publishing.	Improve access to information and enable individuals to publish by changing publication and subscription policies. Promoting best practice and improving quality and reliability of publications. Encourage debate and advocate.	Knowledge dissemination	[52 ,90 ,91]
Civil Society and Media	Newspapers, Radio, Community Advisory Boards, Specific interest groups e.g. Water Aid	Long history of unrequested moderation role but more recent formal inclusion in decision making.	Advocacy and public moderation. Filtering and amplifying messages. Can be condition specific or aimed at general issues	Advocacy and advisory roles at local national or supranational levels. Can redefine boundaries of acceptability and ethics. Can also provide bottom-up innovative approaches. May also mobilise resources.	Varied. Normally knowledge dissemination and communication. Increasing involvement in knowledge utilisation and some creation.	[31 ,86]

2.3.3 A brief history of health research capacity development pre-2000

Although papers published pre-2000 were excluded from this analysis, many current papers provide histories of HRCD. These various accounts detail the trends in HRCD strategy. These trends and the reporting of multiple histories can be viewed as socially, politically, financially and context driven. However, they also represent iterative learning and accumulated knowledge over many years. Since this learning forms the foundation for the strategies used post-2000, we include a brief history summarising the dominant understandings. From this we can begin to consider “what works”?

The earliest paper identified that called for science research towards capacity development was Odhiambo in 1967 [92]. During the 1960s most donors believed the path to development lay in financing basic infrastructure such as electricity, transport and telecommunications. Sector emphasis was on agriculture, finance and industry to ensure economic development. It wasn't until the 1970s that there was a move from physical capital to human capital, which brought with it the fight against poverty and an interest in health, education and environment. Eventually the international community began to view human development as the primary goal and economic development as one tool in achieving this goal [8]. Supra-national organisations began to get involved in HRCD during this period. The first being the Canadian International Development Research Centre in 1970 followed by the Swedish Agency For Research Cooperation With Developing Countries in 1975. Also at this time, the UN, World Bank and WHO formed the International Special Programmes for Research and Training; one for tropical diseases (TDR), and one for reproductive health (HRP). Early support was typically given to national research

councils and ministerial agencies [12] or involved technology transfer rather than developing local capabilities [13]. In 1978 the Alma-Ata Declaration was signed by 134 states, firmly placing healthcare on the international development agenda.

By the mid-to-late 1980s it had become clear that research councils and ministerial agencies did not have the capacity to effectively set priorities, distribute aid and develop capacities at lower levels [12]. Technology transfer failed due to a lack of local expertise and inadequacies in maintenance. Thought leaders (individuals or organisations that are recognised as an authority in their field) began to advocate for transfer of knowledge and skills rather than technology [13]. This led to training individual researchers through post-graduate scholarships in North America and Europe. However, individual scholarships were also not as effective as hoped. Newly graduated Masters and PhDs did not return home or left after a short period due to a lack of opportunities, poor pay and working conditions [76]; this led to donors shifting to institutional level development in the hope of building institutions that could create local capacity. However, without skilled human resources to man the institutions, little could be done. By the 1990s development agencies realised that support needed to be more comprehensive and include individuals and institutions [31].

The 1990's were characterised as a "revolution" in health research [8] with a great degree of international commitment [3]. The United Nations Millennium Development Goals spurred many international donors, notably the newly formed Bill and Melinda Gates Foundation, to begin investing in health care and research in LAMICs. In an effort to pair institutional capacity with individual capacity [83], development agencies focused their efforts on specific projects run by university departments and research groups. Many networks that brought together

stakeholders from public and private sectors were also formed. These initiatives vertically targeted high profile issues which could not be tackled by single institutions [10 ,17]. This led to development efforts supporting specialised individual and institutional level development that would develop research projects, rather than general capacity [38]. By 2003 around 70 Public Private Partnerships had formed [8]. These approaches, to a large degree, became the norm until the mid-2000s and still persist today.

2.4 Findings

2.4.1 Source attributes and characteristics

Table 2.5 shows a breakdown of the contributions by author attributes and key characteristics of the papers. The greatest number of articles came from LAMIC academic and healthcare institutions (31.3%), closely followed by HIC academic and healthcare institutions (29.6%). Contributions from funders were very low (0.8%), and industry and civil society were absent, potentially reflecting the sampling from academic databases. Europe was the greatest contributing region (32.9%) followed by Sub-Saharan Africa at 23.8%. Contributions from Latin America (2.5%), Middle East (1.7%) and North Africa (0.8%) were very low. Although most articles were concerned with capacity development across all LAMICs (42.1%), Sub-Saharan Africa dominated the regional specific discussions (34.6%).

The main basis for viewpoints was opinion, debate or personal perspectives (34.2%); sharing experiences represented 21.7% and empirical work 20.8%. Of the 50 articles that were empirical, most had limitations that made it difficult to form firm conclusions. However, there were some comparative case-studies [30] and large mixed-methods studies [26] that were used to make recommendations. Most

conference reports and organisation documents did not include the basis for their recommendations.

HIC and LAMIC academic and healthcare institutions had similar basis for their viewpoints, the majority being opinion-debate-perspectives (35%/41%), then empirical (31%/27%), then experience sharing (17%/23%). The empirical papers (n=50) were dominated by topics investigating individual level HRCD (40%), with a much fewer number investigating partnership-networking-consortia (16%) and research challenges/opportunities & operations (12%). Although clinical trials were a key discussion point in 20.5% of papers, they made up only 8% of empirical papers. The majority of these were concerned explicitly with international trials or trials in general. Only 3 articles (1.3%) dealt with local clinical trials, none of these were empirical, and all were from LAMIC academic and healthcare institutions.

Table 2-5 Breakdown of contributions by author attributes and key characteristics of the papers.

Global organisations, consortia and networks, public-private partnerships and NGOs have been merged into one actor category because sources did not fit discreetly into categories.

Rank	Author's Actor		Location of first author's institution		Region of development interest		Main topic of development interest		Main Disease of interest		Trials as key point of discussion		Basis for viewpoint	
	Category	% N=240	Region	% N=240	Region	% N=240	Topic	% N=240	Disease Group	% N=240	Trial groups	% N=240	Category	% N=240
1	LAMIC Academic and Healthcare Institutions	31.3	Europe	32.9	All LAMIC countries	42.1	Multiple broad issues discussed	24.6	Not disease specific or address multiple	72.5	Trials not a key point of discussion	79.6	Opinion, debate, perspective	34.2
2	HIC Academic and Healthcare Institutions	29.6	Sub Saharan Africa	23.8	Sub Saharan Africa	34.6	Individual Level development	15.8	HIV	6.3	International trials	13.8	Experience report	21.7
3	Multi-laterals	10.4	North America	13.8	South Asia	10	Partnerships Networking, Consortia	15.8	Malaria	5.8	Trial type not clearly specified	5.4	Empirical Research	20.8
4	Global Organisations, Consortia & Networks, NGOs and Public-private Partnerships	8.8	South Asia	10	East Asia	6.7	Operational Challenges,& Opportunities	11.3	Other	4.6	Local trials	1.3	Literature review, summary or synthesis	7.9
5	Academic Journals	5.4	East Asia	9.2	All Asia	2.9	System approaches and Macro level development	9.2	Mental Health and Addiction	2.5			Proceedings or conference report	7.5
6	LAMIC Governmental	4.6	Australia	2.9	Latin America	1.7	Agenda and priority setting	6.3	Maternal Child Health and Paediatrics	2.5			Organisation document	4.6

7	LAMIC Funders, Research Councils and Institutes of Health	4.6	Latin America	2.5	Pacific	0.8	Institution level development	5.4	Tuberculosis	2.1			News report	3.3
8	Bi-laterals	2.1	No specific region given	2.1	Middle East	0.8	Monitoring and evaluation	2.9	Non-communicable diseases	2.1				
9	HIC Research Councils and Institutes of Health	2.1	Middle East	1.7	Central Asia	0.4	Research and Development	2.1	Dental or oral health	1.7				
10	Private Foundations or Charity Funders	0.8	North Africa	0.8			Ethics and regulations	1.7						
11	Industry	0	Pacific	0.4			Knowledge cycle	0.8						
12	Civil Society and Media	0												

2.4.2 Meta-narratives in health research capacity development

2.4.2.1 *Power relations in research and capacity development*

Power relations in research and capacity development was the most common narrative in this literature, being present in 29% of all papers. This narrative began to appear in the early 2000's and has continued to the current day. It encompasses the issues arising from the perceived dominance of HIC institutions over research conducted in LAMICs. The majority of these voices come from Europe (39%).

A key concern of this narrative is that research agendas and priorities in LAMICs are set more by international funders based in HICs than by national institutions. The common term to describe this is “donor-driven policies” [20]. This is argued to erode national sovereignty and create research priorities that more closely match funder agendas than the country's needs [31 ,93 ,94]. Several papers argue that much of the research done in LAMICs may not be of any use to “beneficiary” countries [17]. This situation may be driven by 2 main factors. Many authors suggest that the research agendas are set incorrectly because of a mistaken understanding of local needs and realities, often blamed on insufficient inclusion of local stakeholders [40], or insufficient situational analysis. Examples given in support of this include “spotlight issues”, which receive support regardless of relative need [20], and “stove piped” funding, meaning to only narrowly fund a particular programme without addressing wider needs [4 ,38]. Alternatively, a group of more critical authors argue that the research agendas may be deliberately set incorrectly by funders to pursue research which is self-serving [95] [24] or politically driven[5]. These authors cited funding rules that require collaboration with research institutions from the bi-lateral donors' country [12] and the USAID mission statement

describing themselves as an “agency that conducts foreign assistance and humanitarian aid to advance the political and economic interests of the United States” (Poole 2002, p156 in [96]).

A subsequent concern was that research conducted in LAMICs is predominantly led by researchers from HICs, with little or no involvement of local researchers or local institutions. Such research models stem from the fact that the majority of investment comes from HICs, leading to the situation of “he who pays the piper calls the tune” [31]. A common example of this are the “annexed” research sites, which are based in LAMICs but most research and expertise is expatriate-led [40], or “parachute” research where foreign researchers collect data in LAMICs but all further work is conducted back at home institutions. As such, local staff frequently have only operational roles in these research models [37]. Such “semi-colonial” [40] research, as some have coined them, were prevalent until the millennium but have become increasingly unacceptable [97 ,98].

Perennial capacity constraints mean that collaborative research between LAMICs and HICs is often essential to address many health concerns. As such “North-South” collaboration between HIC and LAMIC research groups has been described in this literature as the mainstay of HRCD since the early 1990s [12], although several collaborations have a much longer history [17]. However, concerns have been voiced regarding the equity of benefits arising from collaborative research [5] as many people feel that North-South research comparatively disadvantages the LAMIC partner [23 ,33]. Combined with the often absent feedback of findings, this situation led such “North-South” collaborative research to be described as “treating Africa as a repository of raw materials for expatriate-driven research” [23].

These concerns are observed in this literature as emerging around the late-1990s and led to the development of guidelines for research partnership with developing countries. To reflect this change, there appears to have been a rhetorical shift to using the term “partnership” to describe collaborations that were equitable [40]. In essence, proponents argued that partnerships should be built on mutual trust and shared decision making, national ownership, early planning for translation of research findings and development of national research capacity [40]. Since then there has been much attention to correct the sharing of benefits. Importantly this has led to increasing expectation that all partnerships should have capacity development at the forefront [33]. However, despite discussion for well over a decade, it appears that a good proportion of the international research community still feels that partnerships are not yet equal [33 ,46 ,97], nor can they be until the current power divide is addressed [5]. Some authors argue that capacity development is seen as a one-way affair by HICs who consider themselves expert patrons and LAMICs as inexperienced recipients [33], negating the notion of partnership [96]. Others suggest that the power divide this creates makes LAMICs vulnerable in negotiations by being unable to refuse external actors demands or bargain for a fairer deal [5 ,53 ,99].

In an effort to adjust the power balance, and therein the balance of benefits in collaborative research, there have been conscious efforts towards recognising local research capacity in LAMICs. This change is evidenced by the international community recognising the extant expertise of LAMIC’s [31] and by LAMICs increasingly asserting their rights and ownership over national issues [33]. This change is again reflected in rhetoric through the evolution of the terminology used to describe capacity development. The original term “capacity building”

conceptualised creation of new capacity where none existed. The rhetoric then moved through “capacity development” to the still popular “capacity strengthening” and “capacity enhancement” [31], conceptualised as recognising that local capacity exists, albeit weak, and helping it to grow. Since the mid to late 2000s the terms “Capacity Utilisation” [100], “Unleashing” and “Releasing” [31] have been used to emphasise that extant capacity, rather than being weak, is powerful only requiring assistance to make the most of it.

Despite some evidence that North-South collaborations are more fruitful than exclusively local projects [101], many authors now propose that research and capacity development in LAMICs should be locally-led and owned [31 ,40 ,47 ,48]. These arguments do not exclude collaboration and are also not solely based on political correctness and equity. Rather, proponents present locally-led research as having concrete impacts on policy and practice [15] because local researchers have the best understanding of evidence gaps [40] and can present research to policy makers with an understanding of the political and cultural context [43]. They also point out that local studies are more commonly driven by a national agenda [41] and address applied implementation topics which are considered to have a more rapid impact than the novel product trials typically done by foreign groups [40].

Accordingly, most stakeholders now agree that research and capacity development should, at a minimum, include the local research community in the design and conduct of research studies [102]. Development actors are also advised to be more sensitive to the power dynamics they create and ensure they strengthen, not weaken, the role of national governments by responding specifically to their priorities [31 ,48 ,103] and including the “recipients” in any agenda setting [4]. However, others argue that this situation will inevitably continue so long as foreign

countries are the majority financers of research in LAMICs [104]; only through greater national investment and commitment will LAMICs have a stronger voice to make relations more equitable [22 ,23 ,105].

2.4.2.2 Demand for stronger links between research, policy and practice

From the mid-2000s some authors began rejecting narrowly conceived research in favour of knowledge creation that paid explicit attention to the wider knowledge cycle and research impact [72]. This emerged due to concerns that much research was failing to be translated into policy [32 ,99]. Narratives arguing for stronger links between research, policy and practice to improve research impact were present in 16% of sources.

Many authors contributing to this narrative felt that part of the problem was the excessive focus on disease specific research; instead more research with wide portfolios [38] of basic and applied research [106] including social science [28 ,107] was required. In particular, systems approaches have received more attention because systems determine the effective adoption and delivery of a service [99]. Accordingly, applied fields now deemed to be highly relevant to decision makers and those that promote sustainable adoption and implementation of evidence based medicine have been emphasised [15 ,36 ,62]. These include health policy and systems research [54], health services research [108], implementation research and operations research [87 ,109 ,110]. These ideas and sectors now fall under the new WHO strategy term “research for health” [111].

Despite these discussions, much research is regarded as uncoordinated and concentrating on a few high profile diseases [38] such as the “big 3”: HIV/AIDS, Malaria and Tuberculosis. The majority of research is critiqued as largely technology

development focused, even though many argue that such research outputs are very low [108] and more lives could be saved by improving service delivery of existing interventions [54 ,65 ,99].

2.4.2.3 Moving towards a systems approach

In line with the increasingly locally-owned, action-orientated and broad perspectives emerging within the literature, the levels at which capacity development interventions are targeted have also changed. Narratives on this were discussed in 24% of sources.

Interventions have traditionally swung between either targeting the individual or institutional level. Individual level interventions were generally deemed most important [83], focusing on training researchers to directly support research generation [10 ,105]. Following “brain drain” and criticisms that training alone was insufficient to encourage good research [45 ,112], professional development and career incentives were added to create a more attractive and rewarding research environment [113]. Institutional development then changed from being a competing or separate approach that focused solely on material provision, to a more complimentary approach designed to strengthen researchers’ ability to generate knowledge by providing an improved environment to retain and support individuals to conduct research [3].

While individual and institutional level approaches are still very popular [20 ,80], especially with thematically targeted projects, system development has recently gained much momentum [27]. Conceived in the 1990s and popularized after the Ministerial Summit on Health Research in Mexico in 2004 [99], system approaches to HRCD are reported to have emerged in response to perceived failings of capacity

development targeted at only one level. Particular weaknesses cited included lack of provision for trained individuals to use their skills, the gap between an individual's training and their development into an independent researcher, focusing on exclusively assisting "high performers" [83] rather than strengthening local institutions to produce and develop their own researchers[73], absence of national bodies to coordinate priorities and develop policy [10], poor alignment of research priorities and translation into policy, and the fragmentation of capacity development stakeholders [24 ,114].

Instead proponents argue that parallel interventions are needed at all three national levels that make up the research system; macro, institutional and individual [77]. Essentially they argue that capacity development at a single level is less effective and sustainable without addressing system wide development [12 ,77] because all the stakeholders and units of the research system are highly inter-dependent [94]. The health research system is generally regarded as having 4 main functions: stewardship and governance, financing, creating and sustaining resources and producing and using research. It may operate at national, regional or global levels [74], although most discussion refers to the national level, and has overlap with other systems including the education system and the science and technology system [24]. Although presented as a highly complex task with long time frames [28], taking a systems approach is said to result in more dynamic capacity development that produces endogenous change, greater local ownership and removal of perennial system barriers [31]. This in turn would contribute to local action and allow countries to effectively target their own health needs [94].

The systems approach stimulated the nascent field of macro level development. This includes creating capacity in: planning and coordinating, management and

administration, governance and priority setting, networking and leadership, translation and dissemination, advocacy, ethics and regulation and monitoring [24 ,111 ,115]. This is all in stark contrast to previous approaches that established parallel structures to deliberately bypass local systems because they were deemed to be chronically ineffective [46].

Systems approaches also transformed the way individual and institutional development was considered. Individual development now encompasses and values a broader range of stakeholders, rather than just research producers e.g. policy makers, administrators, support staff, medical personnel and ethics board members. It also trains and appreciates a wider variety of skills and disciplines, particularly “soft skills” such as organisation, management and leadership[10] and social and behavioural science [28 ,107] and implementation research [65]. Discussion on institutional development now focuses more on the ability to generate, retain and utilise individual capacity through improving curricula, training support, mentorship, and research resources [17 ,116 ,117]. It also argues that institutional development should target the whole institution, rather than favouring individual research groups or organisations within the institutions [107].

However, despite the accepted importance of research systems development, little is known about how health research systems can be formed [94], there are few successful examples and little guidance available [75].

2.4.3 A summary and critique of modern HRCD modalities

Research models that directed funds and technology through, or at least required the involvement of HIC institutions, became the preferred delivery mechanism after difficulties with pairing human, material and technical capacities

[8] in the mid-late 1980s. Ever since this point and until very recently, collaboration with HICs has been near ubiquitous in capacity development modalities. The only exceptions to this are a few unrestrictive grant calls, but they are usually directed towards specific agendas set by HIC donors [20]. The justification for the near obligatory requirement for collaboration with HIC countries is that knowledge transfer and HIC in-country expertise [19] are required to achieve successful development [13]. But despite the enduring and preferential nature of this fund channelling mechanism, it is purported to disempower developing country researchers [104], result in foreign dominated research agendas [40] and too tightly control spending [118]. However, recent efforts to reverse this trend and provide less conditional “basket” funding to national governments have also been criticised because investment often only goes to healthcare since there is no specified budget line for research [52].

Discussions on development modalities are therefore a contentious issue. This is reflected by their discussion being present in 53% of sources. The following sections summarise discussions on justifications, benefits, drawbacks and controversies of the main development modalities.

2.4.3.1 Vertical research projects

One of the earliest and most persistent research models arising from the HIC fund channelling mechanism was vertical research projects [8]. These approaches involve a HIC research collaborator working in a LAMIC to conduct highly applied, normally short-term research projects with narrow objectives [73]. The theoretical advantage of a vertical research strategy is that it maintains focus on a specific scientific mission [18]. This allows the necessary capacity to be developed more

rapidly and can quickly produce research outputs [8] even where major expansion of R&D is required [4]. These approaches now account for the biggest share of health research funding [77]. Examples of these research models include product development partnerships such as The Global Alliance for TB Drug Development, public-private partnerships such as The International Aids Vaccine Initiative, and many commercial or non-commercial clinical trials [34].

Capacity development is often included in these programmes, but development of capacity is usually not the primary objective [115]. Rather it is designed to develop capacities that will benefit the successful completion of the project [17] and result in high quality research outputs [73]. Vertical projects normally have strong expatriate leadership and are often managed by external institutions [73], effectively setting up parallel structures that bypass the local system [35]. Where individual development is provided, it is typically short term and project specific [119]. Therefore, despite expectations that local ownership and capacity development should be at the foreground of research partnerships [8 ,33], this is reportedly often not the case [23 ,37].

Critics of vertical research argue that local researchers often only have support roles [37], samples may be shipped abroad for analysis [97] and there can be little investment in local institutions because they are bypassed [5 ,35]. As such, this research model has derogatorily been called “parachute research” [40]. The project specific nature of capacity development is also argued to result in functional rather than performance capacity. According to Green & Bennet [31], “functional capacity refers to the capacity specific to undertaking particular tasks, while performance capacity, by contrast, refers to more generic capacities that need to be present within a given organization, in addition to an enabling environment, in order for it to

be able to perform optimally”. Therefore critics suggest that when short-term vertical projects finish, research sites and individuals are rarely left with the skills or resources to run their own studies [34 ,36]. Another criticism is that vertical approaches force the research community to work separately on issues that are overlapping [120] and lead to “balkanization” and disintegration of national research systems [10].

Proponents of vertical interventions are however mindful of the fact that there is often a trade-off between quality of research and capacity development [121]. They argue that in the case of health emergencies, investment should be made in excellent research, not excellent capacity development. Furthermore representatives of these programmes have pointed out that they have learnt from past criticisms and now are much more mindful of capacity development [81 ,98]. While the requirement for short term projects, particularly for emergency issues is recognised [8 ,119], the vertical model has been the dominant model [77] for almost 20 years. This would certainly indicate that it has been used in situations that would best be served by more long term horizontal strategies that develop capacity throughout the public research system. While Davey explicitly addresses the need for both horizontal and vertical approaches [8], narratives on horizontal approaches are, by contrast, much rarer in the literature and there appears to be far fewer programmes dedicated to implementing them.

2.4.3.2 Centres of excellence

To go beyond the sometimes extractive and narrow research model of vertical projects and conduct whole research processes and diverse portfolios within the LAMIC partner country, more diverse and advanced institutional capacity is

required. A common modality to achieve this is creating “centres of excellence”. These have taken various forms, but the approach generally concentrates investment within a few institutions that show potential to excel and eventually become high quality self-sustaining sites, rather than thinly spreading investment between many needy institutions [10 ,45 ,122]. As such “centres of excellence” have similarities with a horizontal approach, but their selective targeting of single institutions, rather than system wide development, means that they cannot be considered horizontal.

These models are useful because they increase the likelihood of high quality research and renewed investment in an otherwise challenging environment. However, early forms of this concept were criticised as being “annexed” research sites, effectively led and managed by expatriate HIC staff [123]. Others also argue that they create parallel research structures outside of the national system that further depletes the local resource pool by diverting investment and human resources towards these better funded sites [40 ,46 ,108]. More recent forms of “centres of excellence”, such as those championed by the European and Developing Countries Clinical Trials Partnership, strive for greater Southern leadership and better integration with local research systems [79]. However, they still require collaboration with HIC institutions to access funds.

2.4.3.3 North-South partnership

Another extremely common model resulting from fund channelling through HIC institutions is that of North-South partnerships. North-South partnerships came about in response to dissatisfaction with unequal relations between HICs and LAMICs, particularly in vertical programmes [124]. They are distinct forms of

collaboration because unlike “centres of excellence”, they are usually project specific rather than general institution building, and unlike vertical research they put more emphasis on sustainable research, shared leadership and being mutually beneficial. However, depending on the nature of the partnership, these demarcations can become blurred.

Since the millennium, North-South partnerships and have been heavily promoted by organisations such as The Global Forum for Health Research [3], and in the form of partnership grants by The European and Developing Countries Clinical Trial Partnership (EDCTP) [79]. Such partnerships are said to be responsible for increasing resource flows to LAMICs [43] and have been advocated for: increasing scientific productivity [125], training of graduates, staff exchange and knowledge sharing, exposure to cutting edge technology [45], strengthening local education programmes and moderate levels of institutional strengthening [3 ,113 ,126]. This is argued to result in more sustainable development [73], greater cost-efficiency and a broader research scope than exclusively expatriate-led or locally-led research could achieve alone [31 ,40].

Despite their popularity, a greater proportion of the literature appears to be dedicated to problems with North-South partnerships than their benefits. Many authors feel that too much power still resides with the Northern partner and too few benefits are accrued by the Southern partner [23 ,33 ,46 ,97 ,101]. Some even argue that partnerships can retard local development [31] because the LAMIC partner may receive little financial benefit, go unrecognised in publications, and release intellectual property rights [23 ,33]. One potential reason for these failings, is that despite a plethora of explicit guidance and advice for entering into partnerships [33 ,40 ,76 ,83 ,127], not all partnerships may be based on good faith. Given the volume

of partnership grants, HIC groups may only embark on partnerships to access these funds and see the LAMIC partner as a means to an end [43]. Equally, given donor requirements for a Northern country partner [12], LAMIC partners may have few options but to collaborate with Northern institutions [128]. HIC partners may also make only token efforts to develop LAMIC partner capacity, preferring to budget most of the grant towards their own institution [43] and concentrate on research outputs rather than capacity development [31]. Another reason for the failings is that despite good intentions, mutually beneficial partnerships are difficult to maintain [45].

Proposed amendments to this situation have involved changing dynamics of North-South partnerships to be driven by Southern demand [17], led by Southern institutions [31] or building more South-South partnerships [47]. However, LAMIC scientists appear to be less enthusiastic about South-South partnerships than the European discourse suggests [129], presumably because working with another under-resourced institution is not appealing. Furthermore, proposed funding for the South-South partnerships still points towards HIC countries [130], so true Southern ownership and independence may well be questionable.

2.4.3.4 Networks

Discussion on South-South partnerships has mainly related to Africa, and mostly involves setting up cross-African collaborative networks [25]. However, the rise of networking as an alternative research model is by no means limited to Africa.

Networks and consortia models emerged in the mid-1990s. By the mid-2000s they had become a phenomenon to tackle whole programmes of research [17] and are now very popular with funders [17]. Actors adopting network models are highly

diverse and can sometimes be hard to separate from partnership models or vertical programmes. However, they all involve linking multiple research departments, groups or institutions to form networks. In this way they can be seen as complex collaborations between multiple actors, and have a flatter organisational structure with less dominant leadership.

Networks are considered advantageous because they not only avoid leadership controversies, but also move beyond traditionally competitive and individualistic attitudes to work together on common issues. Therefore they are useful to coordinate attempts to address shared issues at regional or global levels [67 ,131]. Indeed, it is the increased sense of global perspective [23] and shared vulnerability to threats that have reportedly driven several networks [18]. Because networks facilitate information exchange and pooling of resources to achieve a critical mass [132], they are seen as particularly important where groups may be isolated [133] or when one group alone would have insufficient capacity to address an issue [134]. Networks are also thought to: help focus on common research priorities [17], promote harmonisation across regions [135], increase knowledge exchange and speed diffusion of innovations [75], encourage sharing of experience [24], forge long term relationships [133], increase chances of sustainability [8] and include traditionally external stakeholders such as NGOs [136].

Despite networks being promoted as a gateway to South-South partnerships [25], they are usually endeavours between LAMIC and HIC research groups working on highly thematic research projects [17]. While these networks are valued for the aforementioned reasons, some authors point out that only connecting between North and South means that LAMIC groups remain isolated from each other [133]. Furthermore, focusing on research groups, not institutions, means that

system development is ignored. However, recently there have been efforts to create cross-LAMIC [105 ,132 ,137], multi-disciplinary networks [16]. The hope is that these local networks will foster increased capacity [16], indigenous ownership [25], dynamic research communities [45], sustainability and self-sufficiency [8].

2.4.4 Strengths and weaknesses of HRCD efforts

Despite these long standing discussions on the various HRCD modalities, there was little information reported in this literature on the strengths and successes of development programmes. Broadly, capacity to conduct health research in Africa has increased considerably since the millennium [33] and there remains great potential to leverage further growth out of current gains [115]. This is best exemplified by increases in the number of clinical trials conducted in LAMICs [138 ,139] and reports of enhanced trial capacity [34] particularly in laboratories [140] and quality standards [63 ,98 ,141]. Such institutional strengthening has helped reduce brain drain in specific cases [142]. Furthermore, although some countries still lag behind in regulatory and ethical review capacity, many LAMICs have made great progress [143 ,144]. Given the apparently greater local inclusion and leadership in collaborative trials [27 ,55], one could hope these gains are sustainable.

The increase in research capacity has likely been driven by recognition of the importance of health research over the last 20 years [8], a revised strategic focus [15], and the expansion of networks and partnerships for addressing research needs [16-18]. However, it is not possible to assign causation due to the lack of monitoring data. In Africa positive outcomes have been recorded in terms of increases in the quality and quantity of published research [17 ,142 ,145], but their

connection to inputs and outputs is not established [14]. Outcome data from other developing country regions is even sparser. This review found that many papers failed to consider theories of change or elaborate why and how successes were achieved, and there was almost no evidence on the best ways of supporting local capacity [54] [55].

This paucity of monitoring and evaluation data is a recognised problem [17]. Operational research and sharing of on-the-ground experiences is thought to be a useful resource, but with the exception of a few good examples [62 ,146], little published material on operations is thought to exist [147]. Although in this review 10% of papers discussed challenges opportunities and operational issues, the sources mostly only explained challenges or presented future opportunities without linking them to operational lessons. This makes it hard to learn from previous efforts [17].

There was wide agreement by authors that HRCD efforts are rarely evaluated [77] and impact assessment methodologies are weak [8]. Reasons given for this are the long time-lags taken to achieve objectives [68], outcomes such as organisational culture are difficult to measure [68], there are no commonly agreed indicators [61 ,115] and most evaluation data is not published [14]. Authors of previous reviews also point to a clear lack of conceptual frameworks for implemented strategies [47], which made selecting monitoring indicators difficult [17]. This is exemplified by our source contributions; over half the sources broadly discussed collaboration, but only 8% specifically discussed how it could be used as an enabling strategy. To remedy this situation, guidance on planning and implementing M&E for health research has recently been developed [48], and one

research group provides online resources to help record, share and formalise tacit knowledge into operational guidance tools [36].

Other authors highlighted that significant capacity gaps remain in many LAMICs. In particular, while clinical trials have generally increased, more complex early phase studies are still lacking [148] and there are too few quality research sites to meet needs [139]. Furthermore, the vast majority of development goes towards international collaborative research meaning local investigator-led studies are largely ignored [63]. This is evidenced by the fact that only 3 papers in this synthesis were dedicated to locally-led trials. Despite increases in some capacity indicators, translation of findings into policy is an enduringly difficult outcome [17, 21] and LAMIC leadership and authorship in studies is said to still be too low [54]. Combined with reportedly insufficient political buy-in for strengthening investment in health research [22] [12], concerns have been raised over the sustainability of capacity development. Several authors point to an urgent need for longer term projects, planning for sustainability of research staff and services, and exit strategies for research sites [139]. However, little literature explores this [28].

2.4.5 Summary of the barriers to health research in LAMICs

The following findings section summarises the main barriers to health research, as indicated in the literature.

2.4.5.1 *Fragmented and uncoordinated health research systems*

Chanda-Kapata et al. [75] describe the Kenyan National Health Research System (NHRS) as “fragmented, overly competitive and duplicative, lacking health systems-related research or skills, having weak governance and ethical oversight,

and marked by official bodies broadly seen as cumbersome and unable to offer incentives for collaboration and innovation”. This case appears common in many NHRSS in Africa [149], and many other developing regions. In fact, research was described as “fragmented” in 18% of all papers. This fragmentation is attributed to a general lack of coordination between the multitude of national and supranational actors [4 ,10 ,24 ,30].

At the national level, the absence of policies providing strategic direction [52 ,149] means that there are no mechanisms to organise activities around national priorities and few incentives for change [30]. Public-sector bureaucracy is considered to lack ability to effectively pool or distribute resources [30 ,43 ,150], commonly has strong central control [28 ,151], is inflexible and resistant to change [152 ,153], and suffers from frequent leadership turnover [110]. At the organisational level, poor communication, networking and collaboration between actors is seen to result in research gaps, duplicative or competing activities [28 ,93 ,150], and failure to create links with national institutions [32 ,73]. The commonly experienced outcome is that national capacity fails to be strengthened [111] and research does not rally around priority health needs [8 ,93].

2.4.5.2 Limited use of health research and funding allocation

A symptom of the fragmented research system is said to be a dysfunctional relationship between essential actors in the policy making processes, most notably research producers and users failing to interact, communicate, cooperate [25 ,30-32] or even trust each other [38 ,74].

On the research utilizer-side, policy makers often do not have access to or are unaware of research [30], do not demand research, or fail to use it when formulating

policy [25 ,32 ,154]. On the research producer-side, research is often not policy orientated [108 ,111], lacks generalizability [155], does not target key health issues [8] or is unavailable [31]. Research producers generally make little effort to encourage active uptake of findings [32 ,45], but this is argued to be due to frustration with decision makers who lack appreciation for research [156], capacity to understand research [28 ,31 ,151], or may even be threatened by it [72].

Many governments are chronically short of funds, and given the low value attributed to research, they usually prefer to invest health budgets on immediate concerns such as patient care [113]. Accordingly the vast majority fail to allocate the recommended 2% of national health expenditures to research and capacity building [99] and there is little private-sector investment [8 ,152]. This remains the base problem for many research systems [35 ,111], limiting the scope and quality of research that can be conducted [113 ,157]. The shortfall in funding is left to be made up by supranational donations but only a small proportion is allocated to HRCD [17]. Furthermore, the short-term project-based nature of most international funding threatens the sustainability of local systems [30], creates over-reliance on irregular funding [93 ,158] and can exacerbate power relational issues [20 ,45].

2.4.5.3 Underdeveloped regulatory and ethics capacity

Regulatory procedures and ethical capacity have made encouraging progress since 2000, albeit from a low baseline. At that time it was not uncommon for research regulations to be absent in LAMICs and studies to be conducted without ethical approval [75 ,159].

In Africa, it is now common for universities and research institutes to have their own institutional review boards [75]. However, this varies widely and the presence

of IRBs in hospitals may be lower [41]. The quality and capacity of these ethics boards is also highly variable [160]. While some are efficiently run and maintain high quality standards, others may be rudimentary [161], have insufficient expertise to effectively review applications, lack standard operating procedures [41] and have long turnaround times [109]. Additionally, there are often no mechanisms to oversee the quality of ethics committees, which fuels societal worries about participant safety [162].

Regulatory procedures are commonly problematic. In many contexts they may be completely absent, have no real legal backing, or be very limited in scope. This results in unclear laws and limits the functionality of ethics boards [155]. Conversely, some countries have overlapping regulatory bodies, resulting in duplicative approval procedures [144] that cause long delays [148 ,154]. Lacking expertise to effectively interpret Good Clinical Practice guidelines, some regulatory bodies have created overly rigid procedures that hamper research [9 ,148]. Complex studies such as early phase clinical trials are reported to be particularly troublesome to interpret [55].

2.4.5.4 Inefficient administration and research management

Dysfunctional bureaucratic administration is reported to be rife within universities and governmental institutions in many LAMICs [12 ,121]. Administration systems are often archaic and have not kept pace with changing requirements [12 ,154] and the needs of research [28]. Fragmented authorities mean that multiple approvals are required [12], often from unnecessarily senior bodies with no understanding or appreciation for what they are administering [151]. Universities often lack the capacity to administer large research grants and many have no research support offices or dedicated research support staff [28 ,155]. This means that researchers

commonly take on budgeting, administration and legal roles, despite being unqualified. Where local institutions do manage grants, fund disbursement and procurement can be very slow owing to bureaucracy [29 ,130] and poor management, particularly a lack of standard procedures [12 ,121]. In some instances, corruption deliberately subverts the process [20 ,23 ,90] but attempts to reduce this often add further administrative hurdles [28].

The outcome is that grants may be mismanaged and research activities severely delayed [62 ,163]. Frustration with procedures can lead to poor relations between researchers and administrators [155], and working outside the institutional system. The absence of capacity development for administration [62] means that problems persist and local institutions are vulnerable in contractual negotiations [33].

2.4.5.5 Inadequate material capacity

In many LAMICs, a legacy of underinvestment in universities and research institutes has led to insufficient research infrastructure to effectively conduct much modern medical research [25 ,28]. The most commonly discussed material capacity deficits were laboratories and knowledge resources. In some cases, basic utilities such as power and water may also be lacking [29].

While research requiring more basic technology is achievable, projects with grander scope are limited. Despite the need for more vaccine trials in Africa, laboratory capacity to conduct investigational medicinal product trials requires much greater investment [16 ,98]. These studies typically have an array of capacity prerequisites [164], and ever increasing quality requirements put an even greater demand on laboratories and data management capacity [141], drastically driving up costs for refurbishment [34 ,165]. Clinical services also suffer severe constraints,

making clinic based or health service research a challenge [41 ,166]. Inadequate access to the internet, either through insufficient computers or poor connectivity, combined with poor library facilities means that researchers have difficulty accessing essential information [26 ,28].

2.4.5.6 Insufficient or unproductive human resources

Human capacity is arguably the greatest institutional barrier to research in LAMICs [25-27]. The importance of this topic is reflected in the quantity of sources discussing this issue; 19% of papers discussed human capacity in comparison to 13% discussing administration and 10% material capacity. The quantity of trained researchers remains a limiting factor in most countries [25 ,154]. In particular, skilled junior level staff, research nurses [167] and pharmacists are in short supply [19] and staff with trial experience are even more scarce [95]. What is more variable is the quality of researchers and specific skills gaps [83]. These include: statistics and epidemiology [155], data management [153], health economics, health policy [3], bioethics [104], research methodology [162] and English language proficiency [126 ,167].

Many authors suggest that too few researchers are being trained to meet demand [35 ,90 ,153]. In some LAMIC countries, skilled academic researchers represent an ageing group and are retiring quicker than they can be replaced [122 ,168]. This is said to be due to the low priority of research in many educational models [26 ,169-171], meaning that students receive insufficient exposure to research during their studies [172]. This may be caused by limited teaching resources, a reliance on didactic teaching methods [130] or poor integration between science and medicine [173]. Local personnel often have few opportunities

to work in research [55], or because of inexperience they can only take on peripheral roles in collaborations [105 ,113], leading to a vicious cycle of skill deficits.

Limited access to literature is also a common barrier to effective learning [26 ,51 ,154]. Although online and open access information is improving equity in knowledge access, availability of computers and unreliable internet are problematic [27]. Furthermore, there are few opportunities for knowledge sharing, limited access to mentors [26 ,72] and lack of funding precludes attendance at international conferences [157]. Without engagement with recent literature and exchanging scientific information, researchers become isolated from advances in their field [27], lack inspiration and are not able to compete on an international stage [83]. This is said to cause an absence of research culture [30 ,84 ,91], without which critical questioning and entrepreneurship necessary for research leadership may not be developed [12 ,28 ,157]. Therefore, even if “functional” skills are present, “performance” capabilities [31] are often not [30 ,154].

Another part of the human resource problem is that the extant pool of skilled expertise is not being used effectively [8]. Mullan et al. found that at most medical schools in sub-Saharan Africa, less than 10% of faculty members were involved in sponsored research [26]. Although much literature comes from Africa, this issue is a global problem [30]. Skilled academics with leadership and management capabilities are in such demand [26] they often find themselves split between teaching, governance and administration. Without support [162], they often have little time for research [55 ,174]. In many public institutions, low salaries force staff to take on private consultancies, which further reduces time for research [154 ,175].

Individualistic [23] and competitive cultures, common in academia, make teamwork and collaboration difficult or at least unattractive [35 ,152]. This problem is most acute between LAMIC researchers [12 ,23 ,72] and may explain why South-South collaboration is unpopular. Hierarchical structures [147], combined with perceptions that research is necessarily a complicated affair, are thought to reduce junior investigators' confidence to initiate research [176]. Furthermore, where management are unskilled or lack interest in research [73], they may actively discourage research involvement [72 ,130].

This disabling environment and lack of incentives makes research an unfavourable career choice in some LAMICs [73 ,113]. This can reduce motivation to undertake research [170] or lead to “brain drain” [27 ,30]. “Brain drain” occurs when research personnel migrate from local institutions to more conducive environments, mostly HICs. Foreign-led studies also attract the best local staff from government institutions by offering higher salaries [5] in a process known as “donor robbery” [40]. This migration significantly disadvantages nation states and nullifies development efforts [114]. While its importance has been recognised for a long time [40 ,83] and it is widely discussed within the literature (14% of sources), problems still persist [7 ,177]. The key drivers of brain drain are largely similar across LAMIC regions and include: lack of protected time for research [170 ,178], low salaries, lack of career permanency, few career development opportunities [7 ,30 ,118], little recognition [36 ,41 ,84] and frustration with the research environment [43].

2.4.6 Summary of enablers to research in LAMICs

Enablers, despite often being broad and lacking implementation consideration, were frequently presented as solutions to specific problems. However, when

assembling all the suggested enablers into a collection, it was clear that there are a plurality of strategies and components to consider, the choice of which depends on budget and context. Given this long list of options, the potential enablers are presented as a table (table 2.6). The table organises the enablers by the barriers they address, the logic behind the enabler, their implementation strategies and the popularity of approach.

Table 2-6 Enablers to health research capacity development in LAMICs

Barriers addressed	Enabler goal	Enabler	Enabler logic (rationale)	Enabler strategy	Popularity of enabler
Fragmented and uncoordinated research systems	Developing system capacity	Harmonising HRCD actor efforts	• Coordination of funding agendas was called for by The Paris Declaration on Aid Effectiveness [179] • Will prevent actor overlap and reinforce aid effectiveness [12] • Identifying resources and estimating critical mass will permit better planning of investment and prediction of impacts [28]	• Undertake a situational analysis [24] [52] and build on existing assets [47 ,48] • Tracking funding to highlight gaps, overlap and identify resources [180] • Use Planning, Monitoring and Evaluation Frameworks [17 ,48] • Develop research agendas collaboratively [119], possibly through web 2.0 applications [31] involving funders [34 ,116] and LAMIC stakeholders [10 ,79]	Recently gaining popularity. 12% of sources discussed harmonisation as an enabler
		Increase networking	• Identifies resources and reduces isolation through fostering dialogue[7] and knowledge sharing [28 ,181] • Builds trust and understanding between actors [133] • Can learn from others experiences [75] through communities of practice [182]	• Keep a database of research actors to connect activities, identify actors and reduce duplication [43] • Utilise or develop professional networks [142 ,183], especially web-based communities [62 ,184] • Organise conferences and working groups on common HRCD topics [7 ,185]	Extremely popular. 26% of sources discussed networking as an enabler.
Limited use of research and funding allocation		Financing and advocacy for research development	• Without greater investment little research can be undertaken [186] and institutions will weaken [114 ,125] • Greater national investment is required [23] to develop indigenous capacity and assert national sovereignty [45] • Advocacy is required to mobilise funds [22 ,23 ,121] and increase visibility and acceptability of research [34]	• Develop national research priorities [52] to ensure targeted investment [155] • Establish a health research finance system [187] using innovative revenue mobilising mechanisms [45 ,177 ,188] and develop close links with businesses [153] • Provide long-term support [12 ,28] and flexible grants [12 ,118] that permit iterative learning and adaptation [189] • Advocate through common causes [80] and engaging with the media [34]	Very popular. 21% of sources discussed funding and advocacy as an enabler.
		Developing capacity to use research	• For research to be to be a good investment, research producers and users must work together to translate findings into action [47 ,85] • Developing capacity to use research involves ensuring research is useful for policymakers and [108 ,111] that policy makers have the interest [156], and capacity to use it [28 ,31 ,151]	• Build capacities of policy makers to demand [99 ,131] and scrutinise research [190] • Build repositories of evidence for policy makers [182] and use Research-to-Action-Groups as knowledge brokers [182] to package findings appropriately [32] • Create a knowledge translation platform [25] to encourage research dissemination [32], dialogue and networking between research producers and users [15 ,75]	Consistently popular since early 2000s. Narrative present in 11% of sources.

Limited governance & regulatory capacity		Developing governance & regulatory systems	• Legislation is needed to ensure research is nationally acceptable and that rights of participants and scientists are protected [65] • Setting priorities will help align funding [10] and ensure more useful research that meets country needs [17] • Monitoring and evaluation identifies problem, highlights successes to justify funding [114] and improves practice [48] • Regulatory and ethics body investment will speed up operations [160] and increase research involvement [26]	• Work research into a legislative framework [75] and develop national health research strategies [61 ,149] ensuring inclusion of all stakeholders [10] • Develop a research coordinating body [75] or scientific councils [48 ,150] • Clarify regulatory guidelines [123],map ethics review and regulatory capacity [139] and streamline application procedures [123] [139] • Strengthen regulatory and ethical review capacity [62 ,75] and develop robust monitoring and evaluation procedures [10 ,114]	Increasingly very popular. Narratives present in 21% of sources.
Inefficient administration and research management		Develop infrastructure and upgrade research resources	• Quality infrastructure and research resources are required to adequately train and utilise expertise [191] and permit researchers to be independent from foreign support [85] • Without sufficient material resources investigators lose motivation or migrate for better opportunities [50 ,83]	• Upgrade knowledge access resources like libraries [47] and journal availability [47] • Make knowledge resources more widely [104] and freely available [8 ,192] • Improve ICT [3], particularly internet [113] • Ensure stable power and water supplies [143] • Invest in laboratories [16 ,143]	Widely recognised (20% sources) but often neglected due to high investment required.
Inadequate material capacity	Creating an enabling environment for research	Invest in research services, management and admin	• Good governance and management are essential for an enabling research environment [3 ,50] • Streamlining administration will speed up operations [121] , free up investigators time [55] and increase motivation [24] • Grant management, budgeting [28] and contracting are specialist skills [35]important for securing grants [127] and fair research contracting [33]	• Finance and support training of management [48] and research support staff [55] • Set up a research support office [47] and develop information and finance systems [31] to help with grant management, reporting and contracts [121] • Develop transparent and accountable policies and procedures [35] • Careful recruitment and performance appraisal ensures productive personnel are promoted and underperformers are identified [193] • Funding can be generated through collecting indirect costs from grants [26]	Becoming more popular but not widely discussed. Narratives present in 8% of sources.

Unproductive human capacity		Develop an institutional research culture	- Local science communities are essential for productivity [15] - Greater exposure to research can create awareness and acceptance of research as a career [104] for both junior and senior faculty members [174] [172]	- Promote departmental leaders based on research experience [157] - Set up a departmental committee to promote research [194] - Regular journal clubs, research days [194], and seminars develop interest in research [119], promote knowledge sharing and critical thinking [195] - Recognising efforts through research rewards [196] or displaying papers [123 ,149]	Not widely discussed as an enabler. Narratives present in 6% of sources.
		Continuing professional development and incentives	- Attractive career pathways maintain investigator interest in research, attract expatriate researchers home and retain local researchers [83] [195] - Long term career development programmes [119 ,197] encourage trainees to stay in research after courses or projects finish [55]	- Re-entry grants or guaranteed employment for expatriate researchers [197] [142] - Higher salaries or funded research time [26] increase motivation [125] and encourage time to be spent in research not private-practice - Protected research time [125] and long term contracts [73 ,125] increase productivity and motivation	Popular. Narratives in 18% of sources. Strategies used by Gates Malaria Partnership [197] and WHO TDR [83].
		Mentorship and role models	- Provides individual guidance through sharing of tacit knowledge and builds self-efficacy[123] - Stimulates interest in research and builds a research culture [198] - Supports training, career development [199] and juniors to engage with research [104 ,122]	- Support mentors with long term funded positions [122] and recognition [113] - Peer mentors can be useful if experts not readily available [68] - Where mentoring is not available locally, institutional partnerships [10] could help through intellectual matchmaking [72] or short exchanges [23]	Popular. Narratives present in 15% of sources.
		Local, regional or international collaboration, partnerships and consortia	- Scientific linkages can increase productivity [125] of the research environment by providing resources, expertise [3 ,200], training [3] and “learning by doing” opportunities [83] - Facilitates knowledge and experience exchange [25] - Can improve quality of multi-site studies e.g. clinical trials [148] - Care must be taken not to weaken local institutions resources or autonomy by paying attention to power dynamics [35]	- Firm advice on initiating partnerships is scarce, although forming or joining networks [45] and health related associations [201], use of professional websites [36] and other networking [202] has been suggested - Most partnerships follow North-South, South-South [31] or consortia models [16 ,80] but other models are suggested e.g. experienced sites mentoring inexperienced sites [118], collaborations between academics and ministry departments [73] and twinning departments [28]	Despite popularity as a general discussion point, only 8% of sources examined collaborations as an enabling strategy

Insufficient human capacity	Developing a sustainable, independent, critical mass of skills capable of addressing research needs	Value and include a broad range of skills and expertise	- To address multiple research gaps and tailor interventions, research teams with diverse experience are required [10 ,36 ,74] - Complex interventions such as clinical trials require broad skills sets to be successful [34 ,120 ,203]	- Support a variety of research roles: nurses [204 ,205], data managers, statisticians [119 ,142], laboratory management [98], research coordinators, pharmacists, data collectors, IT personnel [155], management and administration [23 ,28] - Support and work alongside a variety of disciplines: epidemiology and statistics [142], health systems and policy, social science [8 ,10]	Increasingly popular since mid-2000s, but only in 9% of sources.
		Sustainable research education and skill provision	- LAMIC graduate training now preferred to HIC country training as more appropriate to context, less expensive, builds LAMIC training capacity and brain drain less likely[83 ,142] - Early exposure to research improves critical appraisal, independent learning, writing and interest in research [178 ,198] - There is a need to review and fill essential skills gaps [47 ,112] - Can promotes sustainable development if training capacity is developed or learning resources are easily accessible[55] - Care must be taken to ensure an enabling environment for returning trainees and avoid brain drain [83 ,85]	- Research principles, methodology and skills should become major components of undergraduate, graduate and continuing education [105 ,119 ,157]. - Develop local graduate training capacity [118 ,142] or use mixed LAMIC-HIC “sandwich” courses [31 ,52 ,119] or research fellowships [175 ,197] - Provide training in major skills gaps: data collection, data management, data analysis and statistics [73 ,112 ,142], GCP [55], laboratory skills [85 ,110], computer literacy [73 ,112] and ethics [16] - Increase availability of remote training from “virtual campuses” via e-technologies [53 ,206], distance learning or e-learning resources [36 ,98 ,119] “Train the trainer” programmes effective at building sustainable capacity [7 ,55]	Extremely popular. Narratives present in 41% sources. Training in data management, analysis, and statistics particularly requested.
		Strengthening research capabilities	Research capabilities are essential for “levelling the playing field” so that LAMIC researchers can compete with HIC researchers [174] and actively engage with the research system and all stages of the knowledge cycle [28 ,48]	Provide training in core capabilities: protocol development [109 ,207], effective writing for grant applications and publication [10 ,28 ,48], grant management and budgeting [52] , administration and translation into policy [115]	Popular (15% of sources) but some doubt remains over benefit compared to formal training [186].

		Direct involvement in research	• Practical research experience during education increases interest in research and critical thinking [178] • “Hands on skills” are important for developing the expertise, experience and confidence to run locally-led projects [19] • Direct involvement develops a sense of engagement and co-ownership of collaborative research [208]	• Supplement didactic training with “learning by doing approaches” [10] e.g. applied research-orientated [72] or “on the job” training [87] • Allowing wider involvement in institutional projects [73] • Exchange visits to advanced research sites to update skills [195] • Pilot or small grants for early stage researchers to gain experience [83 ,174] • Collaborative projects should involve local researchers in the entire research process [196 ,209]	Popularly accepted (11% of sources) but not as common as traditional skills training
		Develop research leaders	• Committed leadership is critical for the long-term success of locally-led research programmes [105 ,123] • Good leaders create a supportive team environment for continued staff development and act as “champions” who can promote their research and advocate for greater investment [27 ,202] • Without strong leadership, development successes can rapidly be lost after the partners leaves [8 ,12]	• Project management and human resource management skills need to be developed [12 ,121]: building and motivating teams, negotiation and forming collaborations [130], mentorship [27], time management [176], networking, communication and advocacy [88] • Provide opportunities for promising trainees to take responsibility within a supportive environment [31] and defined career pathway [177] • Where projects are collaborative, local trainees must be involved in the entire research process [196]	Gaining popularity. Narratives present in 13% of sources. TDR have developed a training course on Effective project Planning and Evaluation [117].

2.5 Discussion

This discussion will consider the review findings in relation to the part 1 and part 2 objectives. The implications of the review findings on the part 3 objectives will be discussed in chapter 7.

2.5.1 Summary

The findings from this literature synthesis could be simultaneously considered revealing, reassuring, and concerning. Mapping the field of HRCD has identified and categorised the diversity of actors involved in HRCD and helpfully organised them by their understandings and actions. This proved revealing, highlighting a strong voice from LAMICs and a movement towards more subtle and encompassing understandings of capacity development. It also objectively presented commonly undiscussed motivations and implicit assumptions of development actors, who despite paying lip-service to widely accepted views of best practice, continue to operate outdated and sometimes destructive research models. Nevertheless, the literature reported that there has been undeniably steady progress in health research capacity over the last 45 years, with significant acceleration post-millennium. Development actors have continuously reassessed their approaches through a cycle of iterative learning and have become much more reflexive of their actions. National stakeholders have taken on greater ownership and are now in a more self-sufficient position. However, despite progress, major barriers to research persist, there remains little evidence on implementation lessons, and until recently,

scant regard has been paid to sustainability of programmes. This makes it difficult to decide on the most appropriate actions for developing locally-led research capacity, especially for locally-led clinical trials because of the near absence of consideration they receive.

2.5.2 The evolution of health research capacity development

Scientific capacity development has gone through various evolutionary stages over the last 45 years, and health research is no exception. However, the revolution in attention to health research during the 1990s paved the way for a new epoch in HRCD. The disparate strands of thinking that separated individual and institutional development have integrated, and increasing attention is paid to assimilating them with the macro level using a systems approach.

This suggests that actors have finally begun embracing the complexity that is inherent in any development activity. ESSENCE on Health Research now describe capacity strengthening as “more than just providing training or distributing manuals; it is a complex process that involves shifts in power, provokes changes in systems and is influenced by factors such as cultural values. These factors all have to be considered when designing capacity strengthening interventions” [48]. As can be seen from the list of enablers, actors now understand there is no panacea or one-size-fits-all model. Instead a plurality of solutions exists, the choice of which depends on the research environment. Therefore understanding the local context through situational analyses is now regarded as essential.

There is also realisation that this dynamic approach must include a greater range of stakeholders, and value contributions from more disciplines; no longer should management and administration be a separate affair of inconvenience. Changes in what constitutes individual capacity are the most obvious case-in-point. Many development actors have moved beyond a focus on high-achieving individual researchers to valuing whole research teams, including traditionally overlooked roles. Training has also shifted from a purely technical base to include wider research capabilities and leadership skills through a variety of traditional, remote and interactive or learning by doing approaches.

This more nuanced, situated and inclusive attitude exhibited by many authors has brought greater appreciation of local capacity and reflection on international relations. HIC development actors traditionally viewed themselves as experts providing one-way transfer of knowledge and resources with LAMICs contributing little but raw materials for research. However, the increasing appreciation for local capacity and home grown solutions, a realisation that Northern organisations are not always correct, combined with LAMICs asserting national ownership has led to a subtle reversal of the power dynamic; northern institutions are considering that they could learn from Southern partners and LAMIC governments are now under pressure to take more responsibility for their research agendas. Many actors now agree that LAMICs should develop their own research models and technologies based on an understanding of their needs and contexts, rather than importing answers from HICs.

2.5.3 Health research capacity development, reality or just rhetoric?

These evolutionary trends represent strong progress in HRCD development theory, but if they are not put into action and the *status quo* continues, they remain only ideals. Examples of this abound in this literature: focusing on a few high profile diseases rather than broad portfolios, donor-led research agendas, compulsory requirements for collaboration with HICs, inappropriate use of vertical research models, setting up parallel structures, and fragmentary competitive research. The purpose of this discussion is not to debate the pros and cons of HRCD approaches; there is already an abundance of this. Rather, it seeks to understand why outdated models that inhibit locally-led research remain the *modus operandi*, even though there is clear agreement that they are bad practice. A good proportion of the reviewed literature recognises this, but the authors are polarised between those who espouse ever increasing rhetoric of equality and independence, and an opposite more pragmatic group that remind the global community that, in reality, equality and local development are hard to achieve and may even retard specific research objectives. However, this literature synthesis brings up the possibility of an alternative path to develop research capacity.

The findings clearly and frequently show that the persistence of flawed development strategies is driven by approaching capacity development within the context of a dedicated research model. Attaching capacity development to individual research projects that prioritise research outputs above capacity development means that institutions rarely receive sufficient overheads to support their overall

activities [52 ,115] and commonly little other institutional investment is made. The short-term nature of most projects also compromises the ability to develop any sustainable locally-led research capacity [73 ,119 ,130]. This means that local systems at best fail to develop and at worst deteriorate [20]. Finally the largely thematically focused nature of research projects means that any capacity building attached to them inevitably becomes multiplicative [115], fragmented, duplicative[10] and uncoordinated [17 ,52], despite overlapping interests and generic requirements [184]. In certain circumstances development projects may even adversely affect each other [8]; a process in business terms known as cannibalisation. This creates a trade-off between doing good research and doing good capacity development. Those prioritising good research place research outputs as the primary goal and assume capacity will be developed implicitly through “spill-over”. “Implicit” capacity development is known to be largely ineffective [28 ,121], yet is it continuously used and organisations that use it claim to conduct capacity development.

The other main alternative is “Explicit” capacity development where capacity development is consciously attempted. There is wide recognition this is a superior approach and is much more likely to improve capacity sustainably [28 ,68]. Unfortunately, because the research component is usually more valued by research actors, it receives greater attention. This inevitably dilutes focus on capacity development, so development initiatives normally become “bolted-on” [47 ,68] as an afterthought; thus making them “implicit” in disguise. This trade-off also makes it

very hard to develop locally-led research capacity, because the goals of the research project are often at odds with what is best for building self-sufficiency; for instance, allowing staff to learn through experimentation and mistakes, and involving dysfunctional institutional services will help develop locally-led capacity but will hinder research operations.

Instead the review findings suggest that conducting research for health development, and developing locally-led health research capacities, must be considered two, sometimes diverging objectives, that must be carefully combined to be effectively achieved. Recognising this leads to a third way; “Dedicated” capacity development. This implies that developing local capacity is as equally valued as the research outputs and should be considered as carefully as the research designs. However, this is likely to require considerable effort and extra resources given the trade-off between good research and good capacity development. This has occasionally be done in an isolated way through centres of excellence and training fellowships, but only very recently has it been implemented using systems approaches. The other option is conducting capacity development separately from research projects which is the approached used by a few, mostly new, development actors. Examples of this include WHO’s Strategic Initiative for Developing Capacity in Ethical Review [210], ESSENCE on Health Research [211] and The Global Health Network [212].

2.5.4 Unknown knowns of health research capacity development

The need for dedicated capacity development may seem clear. However, there appears to be inertia towards considering capacity development as equally valuable as research outputs. One possible reason for this is that it is at odds with some implicit understandings of the purpose and motives for research development. These implicit understandings are, however, rarely discussed in the literature.

In his study of medical research collaborations in Africa, Geissler called these apparent but undiscussed issues “unknown knowns”, describing them as “realities that are open to experience but unacknowledged in public speech and scientific literature” [213]. Rather than being deliberately suppressed, certain topics were actively avoided to allow the enactment of appearances of equality, where inequalities were apparent. Geissler’s theory has traction here because there are many “unknown knowns” of HRCD which serve to stabilise the *status quo*.

For instance: when funding comes from bilateral or multi-lateral funders, capacity development is inherently political, sometimes done with priority consideration for donor country benefit or forwarding of their agendas; doing limited development within research projects prevents charitable responsibilities and mandates from becoming too large and unwieldy; HIC and LAMIC researchers personally benefit more from research outputs than capacity development outcomes; and locally-led research would mean HIC researchers relinquishing the seniority that comes with being the funding partner. While these points are not controversial, they make for an uncomfortable discussion. The problem is that by

ignoring these issues, consideration of how dedicated research capacity development could be implemented is unlikely to receive the attention it deserves.

2.5.5 Strengths and limitations and further work

Health research capacity development has previously been described as “*a risky, messy business, with unpredictable and unquantifiable outcomes, uncertain methodologies, contested objectives, many unintended consequences, little credit to its champions and long-time lags*” [47]. This statement definitely resonates with the findings of this synthesis; while some of the more confusing elements of HRCD have been untangled and general recommendations made, identifying specific strategies within this literature for developing locally-led research capacity has been elusive.

Previous reviews of capacity development have lacked sufficient reflexivity and questioning of assumptions implicit in many strategies [72]. This literature review achieved its first objective to map the field of HRCD and clarify the key streams of thinking. The meta-narrative synthesis successfully embedded contributions within their theoretical context and permitted the integration of diverse qualitative literature that mostly lacked formal reporting procedures or empirical base. Importantly, it allowed the inclusion of voices that are traditionally excluded in other styles of systematic analyses and helped provide broad understandings of development thinking. However, despite the inclusion of grey literature and Google searches, there was a concerning lack of participation from civil society, industry and funders. It was not clear if this was due to lack of publication interest or limitations with the

search strategy. Nevertheless, the main streams of thinking were presented, and this synthesis arguably represents one of the most detailed, inclusive and nuanced accounts of health research capacity development in LAMICs. Importantly it also allows inexperienced research actors to readily access the topic and understand a fairly complete picture of HRCD.

The second objective of this synthesis was only partly successful. The findings challenged traditional thinking, suggesting that commonly used development modalities will find it very hard to develop sustainable locally-led research capacity. General recommendations to support locally-led research were also made. However, identifying concrete actions required to support locally-led research capacity and specifically clinical trials was more problematic. Most articles had a general focus or related only to sub-Saharan Africa, meaning that it is difficult to apply findings to specific contexts or transfer them outside of sub-Saharan Africa. There was also an alarming lack of attention to the rationale behind some approaches, little implementation theory and barely any empirical data on operational lessons, or monitoring and evaluation to guide future approaches. While the popularity of enablers was presented, it was apparent that this is not a reliable indicator of good development practice. Combined with the paucity of papers relating to locally-led studies, it was not possible to draw conclusions from this literature synthesis on the best methods for supporting locally-led clinical trials.

To maximise on the great progress in HRCD theory, this systematic review suggests that stakeholders need to work together, recognising all interests, to come

up with pragmatically actionable strategies based on rigorous empirical research [51]. One option raised by this review is dedicated capacity development. However there needs to be more examination of what this might look like. The key barrier to designing development strategies based on this new thinking is the lack of data. The current experience sharing data resulting from research conducted in LAMICs is a good start, but more research is required. This should be done with the same rigorous attention to definitions, methodology, analysis and reporting standards as any other research endeavour. Locally-led clinical trials are inherently different and more challenging than foreign-led research, but until this DPhil, almost no research or literature explored these issues.

This confirms the importance of the research question in this thesis and suggests that the findings may be important for guiding future research in this area, and that any recommendations produced, although preliminary, will be a useful and novel start. However, to produce empirically-driven recommendations that are broadly useful, widely acceptable and practically implementable, all the study findings need to be carefully integrated and embedded with current thinking on health research capacity development. This will be done in the final discussion chapter.

PART II: METHODS

Chapter 3: Methods

"The truth is rarely pure and never simple. Modern life would be very tedious if it were either..." - The Importance of Being Earnest - Oscar Wilde, 1895

3.1 Theoretical and methodological framing of the study

The theoretical perspective taken in this study is that evidence-based medicine and practice are important. According to Sackett *et al.* "Evidence based medicine is the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients. The practice of evidence based medicine means integrating individual clinical expertise with the best available external clinical evidence from systematic research" [214]. These early principles of using the best available evidence when making clinical decisions now extend beyond individual patient care to improving population health through evidence-based policies [215]. Although not always perfect, such evidence-based practice is widely regarded to be better than not actively searching for or considering relevant evidence when decision-making [214 ,215].

Therefore, within this thesis, health research in LAMICs is considered important because it provides evidence to make better decisions where evidence gaps exist. Furthermore, this concept extends to health research capacity development because strategies to develop capacity should be based on empirical evidence rather than experience, consensus or opinion. This theoretical stance is strongly supported by the World Health Organisation [31 ,51 ,74 ,111 ,182] and other authors [17 ,24 ,52]. Based on these premises, this study seeks to improve locally-led health research capacity development by conducting research to fill the identified evidence gap and propose evidence-based recommendations.

While this theoretical stance is implicit in the study design, a key aspect of this study is to understand participants' perceptions, attitudes, motivations, and behaviours influencing the undertaking of clinical trials. Therefore, there was a need to consciously consider my biases, be open to alternative perspectives, and examine how the research process may be influencing the data collected and conclusions drawn. This was achieved through maintaining ongoing reflexive practice. [216]. Further consideration of this is presented in "Strengths and limitations of the study design" (section 3.12, page 122).

Although evidence-based practice provides a theoretical framework within which to approach problems by identifying evidence gaps and answer priority questions [217], it does not help select hypotheses or specific frameworks to guide study design and data collection. This is usually done by considering existing research, but in the case of locally-led clinical trials, very little previous research has been conducted. Therefore, this research necessitates an exploratory and formative study design in that it should produce findings on which to form theory that can

explain the clinical trial situation within a given context, and provide a theoretical framework around which to compare and contrast contexts.

The study design and analysis were influenced by Robson's book on "Real World Research", in which he presents a pragmatic approach concerned with producing practically useful findings for real-world settings, but also considers methodologies and theory, particularly Realism [218]. It should be noted that this realist stance, which he terms "Realism-Lite", is not a defined Realist Evaluation approach such as Pawson and Tilley's Realistic Evaluation [219] . Rather it pragmatically selects ideas and terminology from different realist methods. This approach was most suitable for this study because it accepts that there is often a paucity of background literature on which to base early research design and questions, and that early stage exploratory research may be necessitated. As such, Robson's "Realism-Lite" is more suitable for answering the formative research questions of this thesis than defined Realist Evaluation methods.

Realism seeks to understand phenomenon as they happen in the field. This is done through *generative causation*, meaning that A follows B because a number of *mechanisms* operate to produce an *outcome* in a particular *context*. While this does not allow definite predictions to be made, it does allow mechanisms that drove past outcomes to be reasoned reductively, often through flexible iterative cycles of research examining *mechanisms*, *outcomes* and *context*. These repetitions are not closely controlled experimental repetitions, but rather repetitions in *contexts* with similarities or differences in *mechanisms* which are hypothesised to influence *outcomes*. This permits the development of explanatory theory, but it is important to note that the term "theory" is used here in the realist sense, meaning "postulating

mechanisms as being capable of producing the events observed” [218]. In-line with this practical approach, this thesis will focus on the most common and severe issues impacting on clinical trial conduct. This is because in most LAMICS, resources for capacity development are limited, so to have the greatest impact, these resources must be focused on high-order problems [220].

In addition to Robson’s book on “Real World Research” [218], this study was influenced by literature that suggested useful general approaches for investigations on health research development. Taking a systems perspective, which is promoted by many influential bodies [10 ,24 ,47 ,99], was very influential to this study and led to a broad “system-wide” appreciation of the issues facing locally-led clinical trials, but also a specific focus on identifying the barriers and enablers at individual, institutional and macro levels. Although systems approaches emphasise that attention to all these levels are needed, other literature suggests that individual researchers are the most critical component leading to research productivity [1 ,115 ,221]. Therefore, the issues at the individual level were given greater attention in this thesis. Additional influential literature included: being systematic [45], using organisational development approaches [222], and the importance of developing conceptual frameworks [47]. This thesis was also influenced by consultation with experts in their relevant fields, which led to the consideration of psychological and organisational change models, where they appeared relevant.

3.2 Case-study design

The empirical research in this thesis was based on a multiple-case-study design. This permits comparison between similar or different cases when replicated in

different contexts. Replication, rather than being a repetition of tightly controlled known variables, is based on a theoretical framework which defines mechanisms within a case's context that are likely to influence the outcomes of interest. By choosing cases that have similar important contextually based-mechanisms (literal replication), or different contextually-based mechanisms (theoretical replication) the influence of mechanisms on outcomes within different contexts may be assessed. This information is then used to refine the theoretical framework and choice of subsequent cases to test the importance of mechanisms in subsequent contexts. As such these multiple-case-study designs must be flexible because the theoretical framework needs to be iteratively developed and this influences the choice of subsequent cases. This approach described by Yin was the guiding principle behind this study design [223] and is broadly in-line with *generative causation* used in Realist research to understand phenomenon as they happen in the field [218].

Although the case-studies may point towards the importance of certain mechanisms, unlike controlled experiments, findings cannot be attributed to specific variables with certainty. However, a controlled experiment would be very difficult to conduct in these circumstances, and controlling of variables would likely produce erroneous conclusions because trial outcomes are highly dependent on their context [24]. Furthermore, case-studies are recognised for producing valuable results for decision makers by providing a “*general indication of where efforts need to be concentrated to strengthen health research*” [30], and developing potential frameworks to measure health research capacity development [14]. D’Souza and Sadana argue that by comparing case-studies, common challenges can be

identified, which facilitates the formation of recommendations by sharing country experiences between stakeholders and directing research more effectively [30].

Importantly, both Yin's perspective on case studies [223] and Realist perspectives [218] accept that for exploratory research topics initial theoretical frameworks needed to guide selection of cases and data collection and are not always available. Indeed case-studies are used exactly because the relationship between the phenomenon and contextual variables are not known. Yin's definition of a case-study explains this by stating: "*A case-study is an empirical inquiry that investigates a contemporary phenomenon in depth and within its real-life context, especially when the boundaries between phenomenon and context are not clearly evident*" [223]. To overcome this problem, Yin recommends conducting pilot research to test appropriateness of methodologies, validate research tools and analysis strategies, and identify targets for further investigation, thereby ensuring that the phenomenon of interest is appropriately investigated. Results from the pilot study can then be used to form a firm theoretical framework which can be the foundation of subsequent larger-scale case-studies [223].

Since the research question of this thesis is also exploratory, it was decided to make the first case-study a pilot. HRCD literature was used to inform this pilot, but full-scale research based on this literature alone was unadvisable because it was not certain if general health research literature was relevant to locally-led trials, since they are considered by some authors to have unique challenges [63 ,66 ,67].

It is worth noting that the multiple case-study design adopted in this study is holistic, rather than embedded. This is because although actors from multiple institutions are recruited, the institutions they belong to are not individual units of

analysis (embedded cases). Rather all participant responses are pooled to build up a picture of the national research system (holistic case). However, where intra-case differences are observed between institutions or professions, these will still be highlighted.

3.3 Case selection

The key selection criteria for case countries were that: they should be based in a LAMIC country, a modest number of clinical trials are conducted in that country, and the output and capacities of research institutions within the country are fairly representative for the region. This ensures that common challenges to trial conduct are present and that there is sufficient trial experience to usefully contribute to the study. It also excludes countries and research sites where there is exceptional research investment and capacity, since the issues faced in these circumstances are likely to be different to normally resourced research in LAMICs. Exceptional situations are usually driven by focused foreign investment such as the activities of the MRC in The Gambia or Wellcome Trust in Malawi. However, they could also be driven by an unusually strong national agenda of research such as India.

3.3.1 Ethiopia

As stated previously, this first case-study acted as the pilot for subsequent research. Since most research capacity strengthening discussion focuses on Sub-Saharan Africa it was decided to first select a country from this region. Ethiopia was chosen because it is representative of a country that conducts a modest number of clinical trials in sub-Saharan Africa. Figure 3.1 demonstrates this by showing the

number of clinical trials registered for each country in Sub-Saharan Africa. Ethiopia had 39 unique clinical trials registered at the time of fieldwork (from first registration to March 2011 [59]). A breakdown of these trials by intervention, leadership and sponsorship type are shown in figure 3.2 as can be seen, the majority are foreign-led drug trials. These mostly investigated the use of approved drugs to optimise treatment.

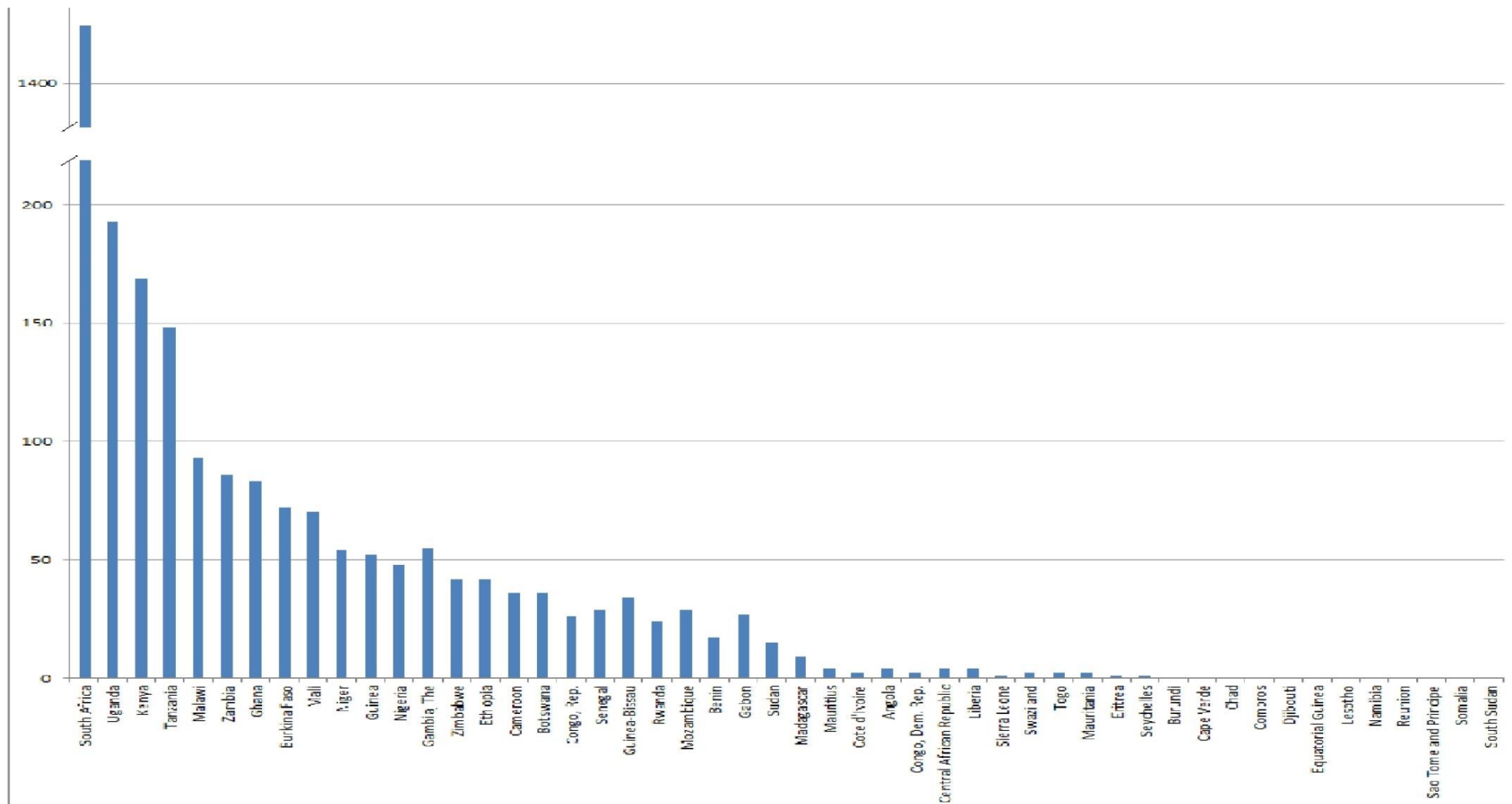


Figure 3-1 Number of clinical trials registered on WHO International Clinical Trials Registry Platform [59] on 10/09/12 by country of recruitment for Sub-Saharan Africa

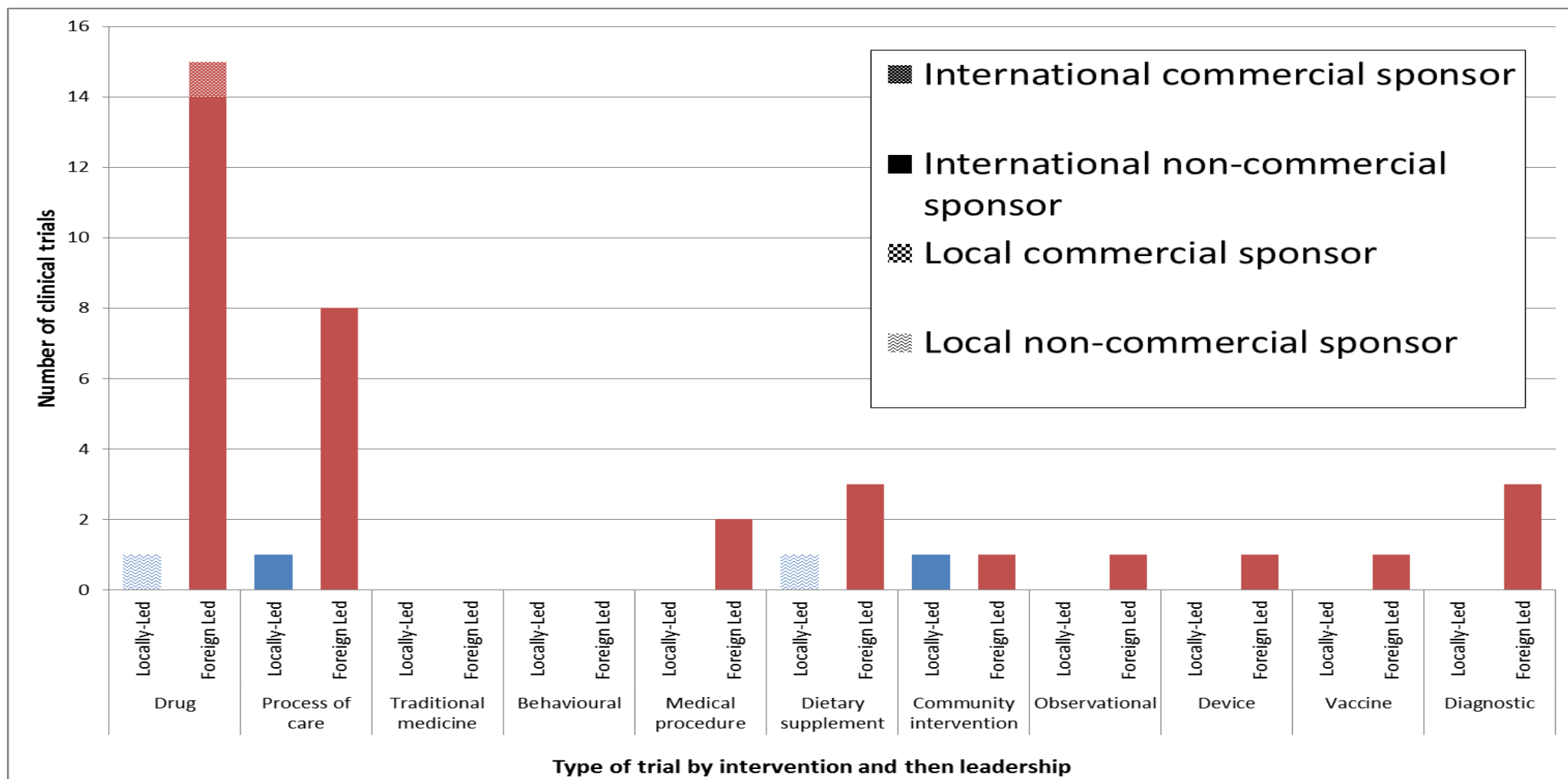


Figure 3-2 Number of unique clinical trials in Ethiopia by type of trial intervention, leadership and sponsorship type;
as registered on the WHO International Clinical Trials Registry Platform [59]. Data correct of at time of field work (March 2011)

3.3.2 Cameroon

The second case-study was a full-scale study informed by the theoretical framework and research experiences developed through the Ethiopian pilot case.

To permit comparability with the Ethiopian case, and thereby have the best chance of demonstrating transferability of findings and explaining divergences, a sub-Saharan country with similar clinical trial capacity and development status to Ethiopia was selected. As such, this was a literal case-study replication.

Cameroon is a reasonable and interesting comparator in these respects. Despite having a lower absolute national income than Ethiopia, given its smaller size and population it is a more affluent country and is classified as a Lower Middle Income Country. Other development indicators are variable; some better and some worse than Ethiopia. A comparison of selected development indicators for Ethiopia and Cameroon are shown in table 3.1. Cameroon had 46 unique clinical trials registered in comparison to the 39 in Ethiopia at the respective time of research [59]. The breakdown of these trials by intervention, leadership and sponsorship type are shown in figure 3.3. As can be seen from the graph, Cameroon has a very similar clinical trial profile to Ethiopia; dominated by foreign-led drug studies. Cameroon is also generally politically stable and safe (within the regions of interest), relatively easy to travel around, and English and French are spoken widely.

Table 3-1 Comparison of development indicators for Ethiopia and Cameroon*Source: World Bank (access date 10th March 2014) [224]*

Development indicator	Ethiopia (year of most recent data)	Cameroon (year of most recent data)
Income Level	Low Income	Lower Middle Income
Population (total)	91.73 million (2012)	21.7 million (2012)
GDP per capita (current USD\$)	\$454	\$1167
Net Official Development Assistance received (USD\$ per capita)	\$36 (2012)	\$27 (2012)
Life expectancy at birth (total)	63 years	55 years
Literacy rate, adult total (% of people over 15)	39% (2007)	71.3% (2010)

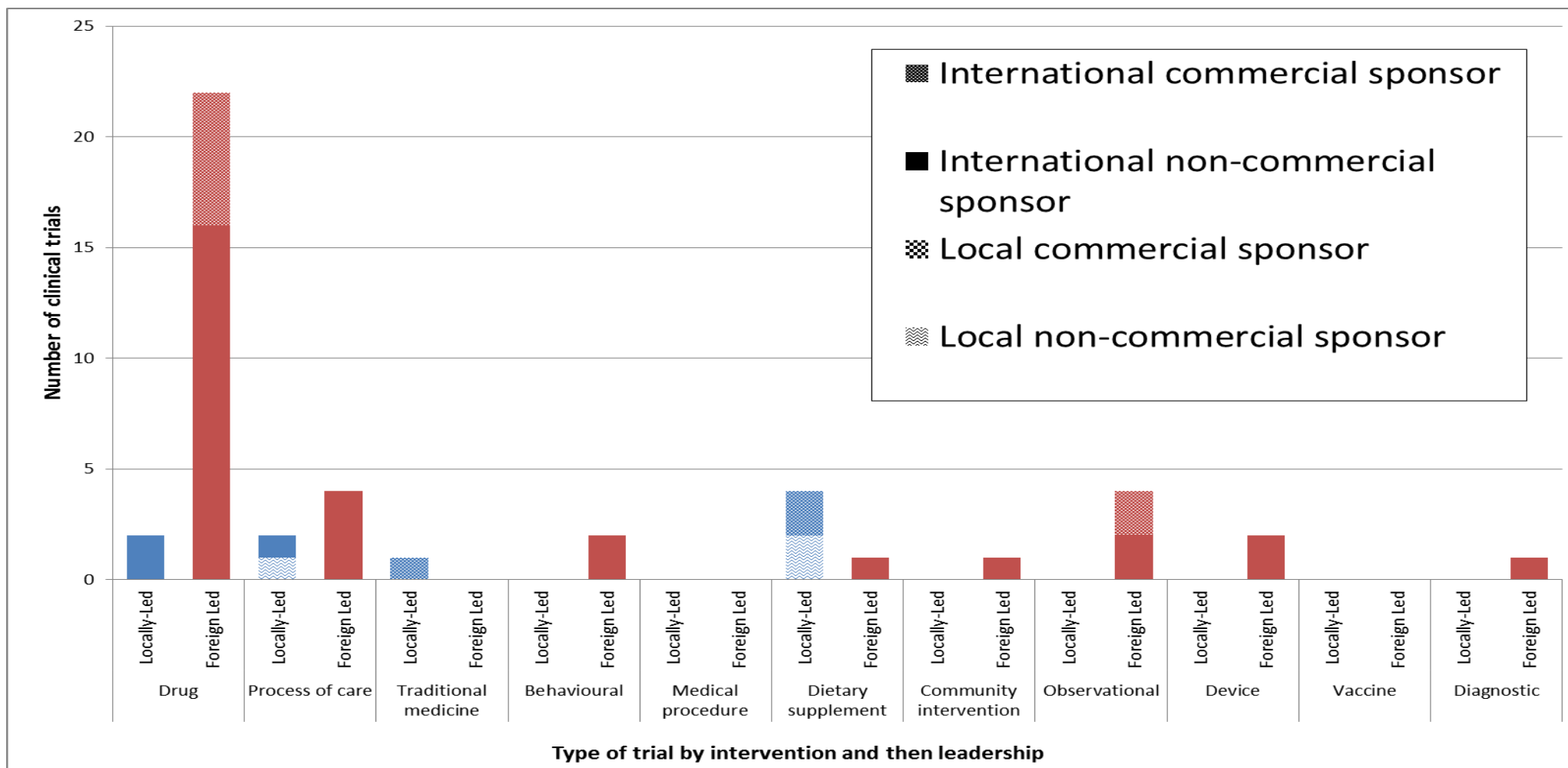


Figure 3-3 Number of unique clinical trials in Cameroon by type of trial intervention, leadership and sponsorship type;
as registered on the WHO International Clinical Trials Registry Platform [59]. Data correct of at time of field work (July 2012)

3.3.3 Sri Lanka

The findings from the Ethiopian and Cameroonian case studies were largely similar, so transferability of the theoretical framework to similar contexts was implied. To ascertain if these findings were more widely generalizable or other mechanisms operated in different contexts, a theoretical replication that deliberately selected a case-study with key differences in its research context was required.

Sri Lanka was selected for the third case-study because it represents an interesting geographical, cultural and research model contrast to Cameroon. Like Cameroon, Sri Lanka represents a country that conducts a modest number of clinical trials, but is far from the research leader in the region [130]. However, Sri Lanka has conducted more clinical trials than Cameroon (126 unique trials from first registration to February 2013, compared to 46 trials in Cameroon from first registration to July 2012 respectively, [59]) and the profile of clinical trials is also different. Unlike Cameroon, the majority of clinical trials in Sri Lanka are locally-led and local non-commercial sponsored. There is also a more balanced intervention type profile (see figure 3.4). Although Sri Lanka and Cameroon are both Lower Middle Income Countries, Sri Lanka has considerably better development indicators (see table 3.2), being ahead of most other countries in the South Asian region despite civil war and political instability [130]. A Sri Lankan case-study therefore presents an opportunity to investigate why differences in clinical trial conduct occur, hopefully identifying best-practices for locally-led research, and to assess if the findings from Cameroon have transferability to a considerably different resource-constrained setting. Sri Lanka is also logistical advantageous compared to other

countries in the region because it is a small country, now largely stable and safe, is relatively easy to travel around, and English is widely spoken.

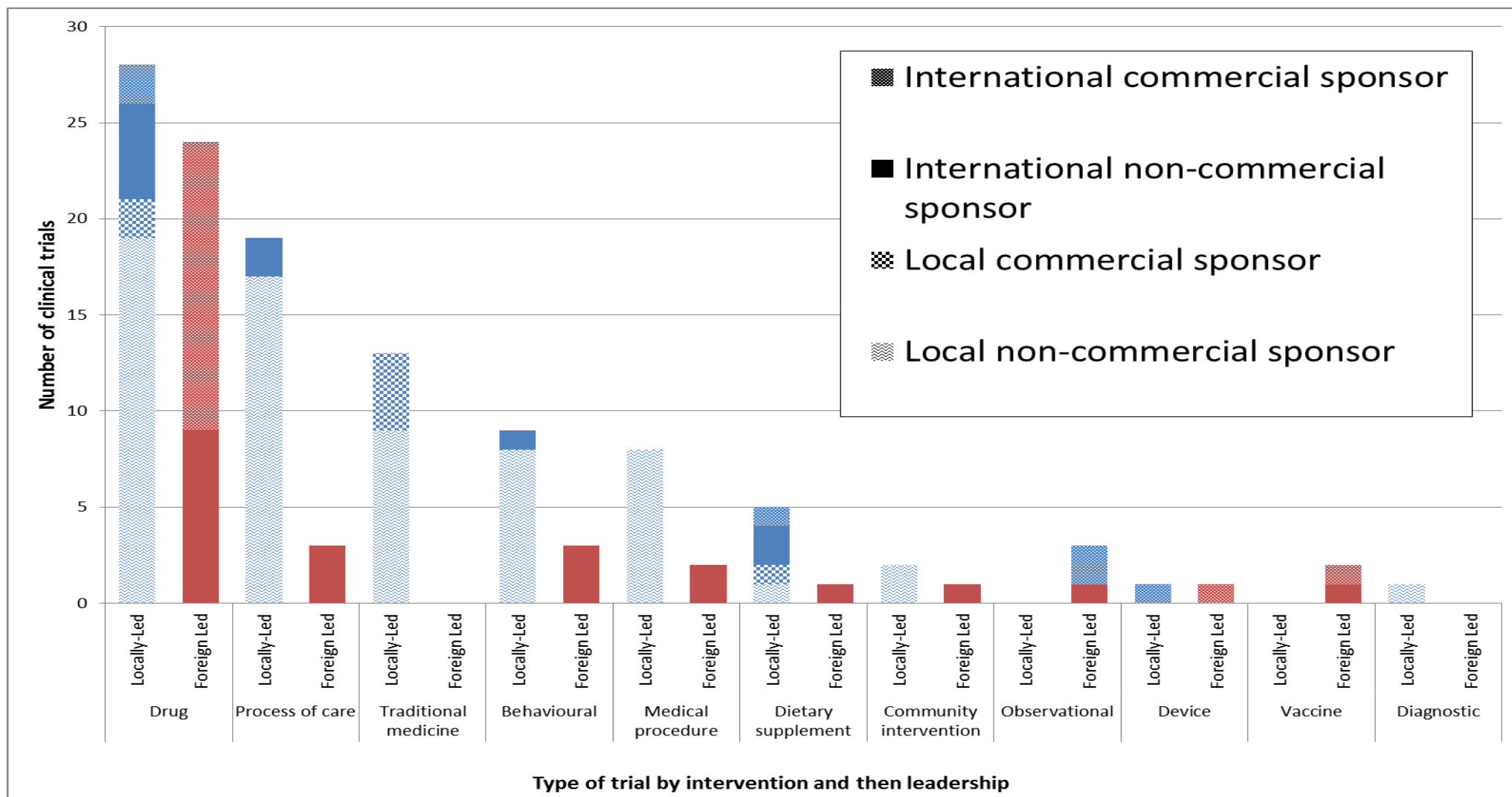


Figure 3-4 Number of unique clinical trials in Sri Lanka by type of trial intervention, leadership and sponsorship type;
as registered on the WHO International Clinical Trials Registry Platform [59]. Data correct of at time of field work (February 2013)

Table 3-2 Comparison of development indicators for Ethiopia, Cameroon and Sri Lanka*Source: World Bank (access date 10th March 2014) [224]*

Development indicator	Ethiopia (year of most recent data)	Cameroon (year of most recent data)	Sri Lanka (year of most recent data)
Income Level	Low Income	Lower Middle Income	Lower Middle Income
Population (total)	91.73 million (2012)	21.7 million (2012)	20.33 million (2012)
GDP per capita (current USD\$)	\$454	\$1167	\$2923
Net Official Development Assistance received (USD\$ per capita)	\$36 (2012)	\$27 (2012)	\$24 (2011)
Life expectancy at birth (total)	63 years	55 years	74 years
Literacy rate, adult total (% of people over 15)	39% (2007)	71.3% (2010)	91.2% (2010)

3.4 Study population and selection criteria

There is a lack of consensus on monitoring indicators for research capacity development [17 ,106], and few accepted frameworks for evaluation [47]. Therefore it was not possible to conduct an objective assessment of the barriers and enablers to locally-led research. Furthermore, authors suggest that too often development decisions are made without local engagement [38] and there must be greater inclusion of those who directly experience issues [65]. Others also argue that a bottom-up approach is needed to fully understand the research context in which capacity strengthening is to be carried out [24]. Therefore recruiting research actors “who grapple with the issues on the ground” [122] to ascertain their perspectives and experiences can be considered a useful source of evidence on which to build an evaluation of the barriers and enablers to local trial conduct.

In the Ethiopian pilot study only health researchers with previous experiences of conducting clinical trials, or those with a strong interest in undertaking them were purposively selected. This was because the limited scope of the pilot case meant that it was important to focus only on actors who had direct and in-depth involvement with clinical trials. However, the findings from the pilot research suggested that selection criteria should be widened to recruit participants with broader range of experiences, particularly those with no experience of clinical trials, research leaders, and decision makers in influential institutions such as regulatory and ethics review bodies, policy departments, and academic administration. This allowed more rounded and specialist perspectives.

In the Cameroon and Sri Lanka cases studies, participants with diverse professional backgrounds and experiences, and those with extensive knowledge of pertinent issues were purposively selected from four broad categories:

1. Locally-led trial teams:

- a. Investigators and trial managers/coordinators who have undertaken locally-led trials within the last 5 years
- b. Trial staff who worked on the investigator's locally-led trials

2. Foreign-initiated trial teams:

- a. Investigators and trial managers/coordinators who have undertaken foreign-initiated trials in the last 5 years

- b. Trial staff who have worked on the investigator's foreign-initiated trials
- 3. Clinicians, academic researchers and healthcare staff who are in a position where they could take on a role in a clinical trial team in the future, but have no current experience of running clinical trials
- 4. Leaders of research groups and academic/clinical departments, local regulators, policy makers, representatives of healthcare and research funding bodies and any other senior stakeholders with influence over clinical trials

In addition to these criteria, all participants had to be legal adults willing and able to give informed consent, and be proficient in spoken English language.

3.5 Choice of methods

Within Global Health there has been increasing pressure to employ qualitative research methods [226] and this has been extended to examining the processes of clinical trial implementation [227] and research capacity strengthening initiatives [17]. The main reasons for this is that quantitative research alone often lacks in-depth consideration of context, and does not provide clear guidance for policymakers on implementation and transferability of interventions. An in-depth understanding of issues in health research is required because interventions inherently involve complex interactions with social and political phenomenon; therefore biomedical problems in the real world are as much constructed through human behaviour as they are objectified issues of study [226]. By employing

qualitative research and social science paradigms researchers can understand the root-cause of issues and offer more complete and pragmatic solutions.

Implementation research on locally-led clinical trials is likely to share many of the same issues. Causes of research inadequacy are complex and nuanced and there is no single solution. Instead pluralities of strategies and enablers are possible but their selection depends on understanding of context. Metric data alone is unlikely to be sufficient for developing an understanding of how better to support locally-led trials because it cannot capture studies not attempted [228] or contextual drivers of failure [229]. Therefore to generate findings that will be contextually appropriate and useful for guiding strategies to enhance locally-led studies, qualitative research methods will be used.

3.5.1 Focus group discussions

Focus group discussions were used to explore issues as a group. These discussions are run by a moderator who poses open questions to a group of respondents who then discuss the point among themselves. The advantage of this method is that it harnesses group dynamics to stimulate discussion, thereby gaining much insight and breadth on commonly experienced issues in a short amount of time and generates new ideas. The diversity of participants also helps respondents to consider their experiences and beliefs more inquiringly. As such they are very useful for exploring cultural values and beliefs and are commonly used in healthcare research [230]. The unit of analysis in this method is the group's discussion rather than individual contributions. This is because while contributions may be assigned

to an individual and related to their background, their expressed opinions cannot be divorced from the group dynamic. Within this study they will be used to explore the diversity of experiences on perceived barriers and enablers to trial conduct.

3.5.2 Interviews

Interviews were used in this study as a method of one-to-one inquiry of respondent's experiences and perspectives. The goal of the interview is to go beyond superficial responses to understand the meanings that individuals assign to behaviour and events. Therefore, where focus groups can uncover a broad set of issues, interviews seek to understand these issues in greater depth and interpret the meaning behind them. The dedicated time allotted to one participant allows the sharing and study of narratives that can help shed light on contextual factors and how respondents prioritise and make sense of the issues explored. Therefore they are useful for focusing down on specific issues that have emerged in previous data collection. They are also useful for exploring matters that are not appropriate for a group discussion such as confidential issues [218].

Interviews were used in this study to elucidate greater detail on specific topics shown to be pertinent to trial conduct. Participants recruited to interviews were selected based on their experience of the specific issue. Since these individuals usually had leadership positions, and therefore their knowledge was often privileged, the privacy of the interview was also appropriate.

3.5.3 Process Mapping

Process mapping was used to capture information on, and relating to, trial operations. Process mapping is an organisational development and quality improvement technique used to create a visual representation of the sequential processes required to complete a project. This is essentially a flow diagram detailing all the individual tasks required to complete a project. These individual tasks are connected by arrows showing the flow from one to another and detailing feedback loops, stops and starts where applicable. Although this can be used as a planning tool, the approach used in this study was retrospective, therefore showing how things are and what really happens, rather than what should happen [231].

Process mapping is ideally a group exercise, where all actors involved in completing a project come together to contribute their experiences of the individual tasks they were involved with. As such it can be helpful for producing a “bigger picture” of the project, yet a detailed view of tasks. It also helps actors to understand others’ views and roles. Because participants are encouraged to “walk through” the project in a logical order, usually from beginning to end, and then reflect if any pieces of information are missing, process mapping is very useful for facilitating recall. Time metrics and other associated data can be added to the process map to give quantitative detail. The main desired outcome of the process mapping exercise is to identify bottlenecks inhibiting completion of the project and identify enablers for improving the whole process as well as individual tasks.

Process mapping has been used to identify the steps and time taken to initiate clinical trials [232]. This approach was very focused on detailing a breakdown of all

the steps involved and the time taken; 296 distinct processes were mapped, but there was little attention given to discussion of the issues. The main aim of process mapping in this study is to record the main steps, processes and times, but also to discuss the key issues in-depth. Through this an understanding of the drivers behind barriers and enablers to trial conduct can be developed. Therefore the main unit of analysis is the group discussion stimulated by creating the process map, rather than the process map itself as an artefact to be studied. This approach is more similar to the process mapping used by the NHS Institute for Innovation and Improvement to consider how patient pathway care can be improved [231].

3.6 Organising collaborations

After preliminarily choosing the case-study countries, it was important to gauge if potential participants were available and interested, and to find a local collaborator. To do this, clinical trial registries and recent relevant publications were searched for studies being conducted in the case country. The Global Health Network networking facility and other informal contacts were also used to find potential contacts from the case country. Potential collaborators were then contacted by email.

A local collaborator was essential for more than regulatory reasons. By selecting a local collaborator with expertise in the area of clinical trials, who is recognised by the local scientific community, and has a number of contacts, they acted as gatekeepers to participants by making introductions and facilitating trust. They also had in-depth knowledge of local regulatory and administrative procedures that

proved invaluable for securing the multiple permissions required, adapted the protocol to be country-specific, and gave useful advice on fieldwork logistics and topic guide adaptation. Finally they reviewed the findings, ensuring that all study reports were representative of the research situation within the country as they saw it.

The collaborators for the case-studies were as follows:

- **Ethiopia:** Professor Fikre Enquselassie, Department of Preventive Medicine, College of Health Sciences, Addis Ababa University, Addis Ababa, Ethiopia
- **Cameroon:** Dr Julius Atashili, University of Buea, Faculty of Health Sciences, University of Buea, Cameroon.
- **Sri Lanka:** Professor Sisira Hemananda Siribaddana, Institute of Research & Development, 393/3, Lilly Avenue, off Roabert Gunawardane Mawatha, Battaramulla AND Dean of the Faculty of Medicine, Rajarata University Sri Lanka

For the Cameroon fieldwork, a research assistant was hired to help organise logistics in Yaoundé. This was necessary because the permissions required were very complicated and required repeat visits. The local collaborator could not do this because he was based in a distant city (Buea). The research assistant was invaluable in securing permissions, and instrumental in identifying participants and organising meetings.

- Frederic Francois Owono Messi, Freelance Research Assistant, PO Box: 20493, Elig-Essono, Yaoundé, Cameroon.

3.7 Research permissions

Once a local collaborator was identified and agreed that the study in the country was feasible, more formal procedures began. All agreements and permissions were obtained prior to the respective research taking place.

In Ethiopia, due to the pilot nature of the study this was more *ad hoc*. Local experts stated that because the study was limited in scope and minimal risk, University of Oxford based ethical approval for the study was sufficient and local regulatory approval was not needed. The local collaborator also did not require a memorandum of understanding or a data sharing agreement.

However in Cameroon, a data sharing agreement was required by the collaborator as mandated by the institutional review boards and the regulatory authority. The study needed ethical approval for the institutional review board where the collaborator was based, and from the National Ethics Committee. Administrative approval was needed from The University of Buea, The University of Yaoundé and the Ministry of Health. These various boards also required a number of other documents confirming my position in the university and that Oxford University Ethical Approval had been obtained.

In Sri Lanka, ethical approval was only required from one university IRB, and administrative approval for the research to be carried out was required by 2 universities. There was also a data sharing agreement with the local collaborator.

3.8 Fieldwork procedures common to all research exercises

All the following fieldwork procedures were conducted solely by myself (Samuel Franzen). This involved gaining consent and collecting completed study documentation, leading and facilitating the research exercises, and taking notes and audio recordings. The only exceptions to this were the research exercises conducted in Yaoundé, where a research assistant (Mr Frederic Francois Owono Messi) helped facilitate the research exercises, take notes, and provided translation support when participants had difficulty finding the correct words in English. However, Samuel Franzen was present and led all the research exercises in Yaoundé.

3.8.1 Recruitment and data collection

Participants were identified by searching clinical trial registries and journal publications for clinical trial investigators based within the case country. Snowball sampling through collaborator and participant referrals was also used. Potential participants were approached by email or phone and were given an information sheet explaining the research

Recruitment and participation in research exercises was conducted at a mutually convenient location, usually a quite private area. Participants were asked to re-read the information sheet and had the opportunity to ask questions. Confidentiality and anonymity were explained, particularly for group discussions because while everybody is asked to keep what is said in the group confidential, it was not possible to prevent other participants from sharing what they have heard. Consent was then

taken to participate in the research, for the research to be recorded, and for their quotes to be used in reports.

In Ethiopia, key informants felt that giving written consent was off-putting and even researchers would be reluctant to sign documents; they felt that written consent should only be used for interventional research or research with greater risk. Given the participatory and minimal risk nature of this study they considered verbal consent to be more appropriate and still ethically sound (as did the Oxford Tropical Research Ethics Committee). Therefore verbal informed consent was gained from all participants Ethiopia. Furthermore, Ethiopian participants said they would speak more openly if discussions were not audio recorded. This was because they would be uncomfortable criticising partners or regulatory bodies while being recorded. One participant explained that this worry was a result of the legacy left by previous authoritarian regimes. Therefore, no audio was recorded for any research exercises in the Ethiopian case-study. Instead detailed notes were taken with quotes noted as near verbatim as possible. Inability to audio record the discussions may have had some impact on the accuracy of notes taken. However, participants were sent a transcript of their discussions to review and asked for email confirmation that the transcript was accurate.

In the Cameroonian and Sri Lankan case-studies, written informed consent was required by ethics boards. Of all the participants who were given the consent form, none refused to take part. Only 5 participants refused to be audio recorded. For the five participants who refused to be audio recorded, detailed notes were taken as near verbatim as possible. These notes were then analysed in the same way as the

audio recorded and transcribed data (see section 3.10, page 112). After consent was obtained, participants completed a demographic information form that recorded their basic personal details, contact information and career information. Questions from the topic guides were then posed. Discussions usually lasted between 1 and 1.5 hours. The upper time limit was 2 hours and issues were explored until no new further information emerged, or participants had to leave for other engagements.

In group exercises, contributions were assigned to specific participants, but given the large number of participants and rapid nature of discussion, it was not always possible to successfully do this. However, this was not a major problem because the main goal of the group exercises was to understand the experiences of the group, rather than the individual.

After each research exercise a contact summary form was completed. This facilitated reflection on the research activities by summarising the important themes that emerged, considering how the procedures could be improved, and whether data saturation had been achieved. Emergent themes identified at this stage were incorporated into future questioning.

3.8.2 Data handling and entry

Research exercise documents, recordings and participants were assigned unique identifiers to provide anonymity and facilitate identification of contributions. The identifier was also used to connect personal data to anonymised contributions. The demographic information form was the only form that recorded personally identifiable information (except the consent form which contained only the

participant's name). All other data collection forms only referred to the participant by their identifier. Therefore it was only possible to connect the participant with their contributions by having access to both forms. First names were verbally used when directing questions but all notes only referred to the participant using their ID number. All notes and audio files were kept on my person at all times or in a locked vehicle or room. Content of discussions were not shared with anyone except the transcriber. Demographic information forms and data collection forms were kept separately.

A "ParticipantLog" Excel spreadsheet was created for entering participant demographic details and recording the participant identifier. Another "MethodsLog" Excel spreadsheet was created for recording research exercises by their identifiers, participants that took part by their identifiers, and the presence and location of any associated research data. Audio files and transcriptions were imported to a computer and the file named after the research exercise identifier. All computer files were password protected.

Audio files were transcribed into Microsoft Word by a professional company; this was fully verbatim, recording hesitations, pauses, utterances, incomplete sentences and interruptions as appropriate. Individual participants were identified by their identifier. Where identification was difficult, the transcriber attributed the comments to "[Unknown]". The transcription was proof-read against the audio file to check for accuracy and any missing or additional information was added.

3.9 Procedures specific to research exercises

3.9.1 Topic guides

All research exercises followed a semi-structured topic guide detailing a number of questions and prompts. Open questions were used so participants could describe their experiences and opinions in their own words.

Questions in the topic guides used in the Ethiopian case-study were based on the limited clinical trial literature and influenced by the wider HRCD literature. However, topic guides were iteratively adapted after each case-study as the theoretical framework was refined. This allowed the incorporation of emergent issues and exploring pertinent issues in greater depth. The topic guides used in the Ethiopian pilot study were considerably adapted for use in the Cameroon case-study because many issues not initially considered as important emerged. However, the topic guides used in Sri Lanka did not considerably differ from those used in Cameroon, because similar issues were found in Cameroon as in Ethiopia. To allow comparison, the initial topic guides used in the Ethiopian case-study and the final topic guides used in the Sri Lankan case-study are included in the appendix (page XVI).

3.9.2 Focus group discussions

Participants with experience of conducting local or foreign-initiated clinical trials, or participants with no experience of clinical trials but in a position to undertake them in the near future, were invited to take part in focus group discussions. Focus groups were normally stratified by experience of running clinical trials to encourage a more

effective group dynamic. However, due to participant availability, focus groups sometimes had mixed categories of participants. There were no notable differences when groups were mixed. There were between 2 and 6 participants per focus group discussion.

A large number of questions were included but it was not expected that all questions would be asked. Rather, appropriate questions were chosen from the topic guide based on participant responses and their personal experiences. The final topic guide used in Sri Lanka had the following format: discussions began with “warm up” questions on the country research needs and clinical trial situation; questions then focused on perceptions of different clinical trial types, operations and running clinical trials, the influence of research cultures, motivation to conduct trials, and the organisational and institutional environment; questions closed by asking participants if they had any suggestions for further research and an opportunity for final comments and questions.

3.9.3 Interviews

Participants in senior positions of stakeholder organisations were invited to take part in interviews. Interviews were also held with other categories of participants if they could not attend group discussions.

Questions in interviews were more specifically tailored to participant’s area of expertise than focus group discussions. The final topic guide used in Sri Lanka had the following format: the interview started by asking about the participant’s job roles then presented the opportunity for an uninterrupted narrative of their experiences

with clinical trials (or other area of expertise); questions then explored their perceptions of different trial types, the research context in their country, stakeholder institutions and their research cultures, and operational challenges; there was also plenty of time to ask expertise-specific questions before the interview concluded with suggestions to improve the research situation in their country.

3.9.4 Process mapping

Investigators with experience of conducting foreign-led or locally-led clinical trials, and their trial team staff, were invited to take part in process mapping exercises. However, the process mapping exercise was only done if senior members of the clinical trial were available. This is because operational mapping requires knowledge of managerial aspects. Since process mapping exercises report a specific clinical trial, only one discreet trial group can take part at a time. Group sizes were normally between 3 and 6 individuals

The process mapping exercise worked similarly to the focus group discussion. However, the topic guide was limited to introductory questions regarding the trial group's current and previous projects, and closing questions on lessons learned, impact of trial experiences and suggestions to facilitate more locally-led trials. The bulk of the discussion time was given over to a passive and minimalist style of questioning. Therefore the topic guide changed very little between case-studies.

Before drawing the process map, participants were asked to describe the main issues that came to mind when they thought about the clinical trial they were mapping. This was done to elicit responses uninhibited by the temporal organisation

of tasks required by the mapping; the hope being that participants' will mention the most important issues first. Process mapping was then explained by drawing a process map of a daily routine from waking up to going to bed. After participants were comfortable with the exercise they were given paper and different coloured pens and encouraged to draw a sequential process map of the trial they conducted from start to finish. The different coloured pens were used to highlight where things went well, badly, and what could be improved with hindsight. Prompts included asking if participants found anything particularly difficult or easy, forgotten operations or time metrics, and strategies that helped them.

3.10 Data analysis

Discussion notes and contact summary forms were regularly reviewed during data collection to identify pertinent themes that should be investigated in subsequent data collection. Handwritten notes were also made on the documents as reminders for the formal analysis. Formal analysis occurred after fieldwork was completed and transcripts had been written. All the transcripts from a single case-study were analysed holistically, building a picture of the research system based on the pooled contributions of participants.

Data were analysed by thematic analysis, through a process of coding data and grouping it into themes that represent coherent units of information believed to be important to the research question. This analytical method is commonly known as thematic coding analysis and is often used in healthcare research [233]. Although considered a more basic form of analysis because it is not linked to a specific

theoretical perspective, it can be very useful for exploratory research [233], where guiding literature and established explanatory models are scarce and it is not known if they would be relevant to the phenomenon being studied [218]. It is sometimes criticised as being largely descriptive, rather than interpretive. However, this is usually when the focus of analysis is too broad [218] or analysis is limited to only labelling content rather than interpreting deeper meanings [233], particularly explaining phenomenon by developing conceptual frameworks or models [218].

As such, approaches and practices of thematic coding analysis can vary, especially in the level of depth and interpretation [218 ,230]. The approach used in this study followed guidance by Green and Thorogood in their book on “Qualitative methods in healthcare” [233]. This is an in-depth (creating many open codes) and highly interpretive (using relationship and modelling to re-integrate the open codes) form of thematic coding analysis that is capable of producing both emic summaries (respondents personal accounts of behaviour or beliefs) and etic interpretations based closely on the data [233] (a scientific observers “culturally neutral” account of the respondents behaviour or belief which can potentially be understood across cultures [233]). This approach was trialled during the Ethiopian pilot case and based on the interpretive nature of the findings it was considered useful and adopted for all further cases. The five iterative phases of the analytical approach used in this study are shown in box 3.1.

Qualitative data analysis packages are a useful tool to help organise and interrogate qualitative data [233]. Nvivo qualitative data analysis package (QSR International Pty Ltd. Version 9, 2011) was used in this study. The clustering,

relationship and modelling functions, were used to help build conceptual models of the mechanisms influential to clinical trial conduct. These were developed through piecing together complementary segments of data contributed from different participants, to identify causal pathways.

All data analysis procedures were conducted by myself. This included reading the transcripts, organising them into Nvivo, and analysing them using thematic coding analysis. As discussed in the methods section of the literature synthesis (page 20), having a second coder would have been helpful for exploring interpretations and developing the analysis, but would not have improved validity through inter-coder comparison because this concept is at odds with the epistemology of the interpretive approach used in this study. Rather, good quality research was safeguarded by making transparent the subjectivity inherent in the findings. Further detail on these procedures can be found in the study limitations section (3.12, page 117).

Nevertheless, it would have been desirable to have multiple researchers review the transcripts and contribute to coding in order to help develop or identify alternative interpretations. However, due to resource constraints this was not possible. As a compromise, Dr Clare Chandler (Social Science DPhil supervisor) reviewed the coding frameworks that I produced and read a portion of the content that was coded. I then discussed and justified my interpretations with Dr Chandler and she presented alternative interpretations or questioned my findings. Through this process I refined the coding framework. Furthermore, all the study collaborators reviewed my interpretations of the results from their respective countries, and

confirmed that the findings were plausible and congruent with their experiences of health research. Therefore, the analytical process was as comprehensive as the study resources allowed.

Box 3-1 The five iterative stages of thematic coding analysis.

Adapted from Green and Thorogood [233]

1. Familiarisation with the data by reading the entire data set (all participant transcripts from a case).
2. Generating codes. Codes are segments of text that represent an interesting unit of information believed to be important to the study question. In this study, open inductive coding was used, meaning that codes were generated from the data rather than being decided in advance, and multiplicative codes were produced until no new codes were identified (saturation). These are then revised and refined iteratively to form a coding list. This coding list is then systematically applied to the entire data set, by reading and re-reading transcripts.
3. Codes are then grouped into themes. Themes are groupings of codes with related characteristics that together have a greater coherent meaning. Once exhaustively completed, themes are then compared again to the transcripts to ensure they adequately represent the whole dataset.
4. Themes are organised into thematic maps or trees. These show how themes are separate or related and if they are hierarchical, essentially placing them in discreet groups. By this point the data is at risk of becoming very fragmented and abstracted from the original content or meaning. To prevent separation from its original meaning, the content within the themes is then re-read to ensure that the theme represents what is coded within it.
5. Themes are integrated and interpreted. This is the “true” analysis phase where themes are compared and contrasted, relationships are identified, causal pathways and concepts are identified and an explanatory account of the data can be generated. This is what is reported in the results section of the case-studies.

3.11 Ethical considerations

This study did not involve any intervention or deception of participants. Rather it focused on discussing professional experiences. Individual responsibility for actions was not normally considered, nor was there discussion about personal issues. Discussed issues were fairly common knowledge and not generally considered controversial. The participants understood the concept of research, their rights, how the findings were to be used and the consequences of participation. As such it was considered minimal risk research and expedited for ethical review by some review boards. The ethical and regulatory approvals obtained for the fieldwork are detailed in the “Research permissions” section 3.7 (page 102).

Participants had the right to withdraw any information shared. There were no direct benefits for respondents from participating. However, it was an opportunity for participants to share their knowledge and experience and contribute to research that was relevant to them. The activities may also have helped participants to identify strategies that could improve the efficiency of their work and highlight areas that needed improving. Although participants were asked to consider their workplace experiences in detail, this was usually a positive and interesting experience and may have contributed to their learning and professional development. Some information was professionally sensitive or could have been covered by confidentiality agreements. As such, participants were reassured that they could share as much or as little information as they liked and may choose not to answer questions or only contribute personal opinions without referring to specific circumstances. All data was kept confidential using the measures mentioned

previously and care was taken to ensure that any details that could identify the participant or their projects were made non-identifiable.

3.12 Limitations of the case-study design

In their review of case-studies on health research, D'Souza and Sadana identify a number of aspects that should be present in all good case-studies: describing the methods used to gather information, combining qualitative and quantitative analyses if relevant, taking a broad perspective on health research, providing sufficient detail and offering recommendations for stakeholders [30]. The design used in this DPhil successfully incorporates and achieves all of these aspects, except that quantitative data was not included. While it would have been desirable to collect quantitative data to permit mixed methods “triangulation”, after consideration it was deemed to be beyond the scope of this DPhil to address, assuming the same quality and level of detail was required from the qualitative component. Instead a follow-up study using quantitative techniques will be considered for future research. This is addressed further in the final discussion chapter (section 7.5 page 352).

Considering an entire country's research system as a single case may also be disputed by some case-study researchers. This is because traditional cases have distinct boundaries that are investigated in detail and the findings largely show a complete picture of smaller detailed cases [223]. While this is important for understanding all the issues within a case in detail, that was not the aim of this thesis. Rather, the objectives were to try to establish the most commonly

encountered, “high order” barriers within research systems that need to be addressed to facilitate locally-led trials in LAMICs. Therefore it was necessary to sacrifice some detail in order to capture broad experiences from the various institutions that make up the national research-systems.

This is a pragmatic approach but one that D’Souza and Sadana say is needed to know where to focus the limited resources allotted to strengthening health research [30]. Furthermore, although there are warnings that pooling data to form a holistic case can lead to shallow and abstract findings [223], the Ethiopian pilot study did not have this problem so it was decided to continue with this design. Subsequent case-studies demonstrated rich, nuanced and contextually anchored findings.

Concerns over social desirability bias are pertinent to this research design. Social desirability bias occurs when participants respond to questions in a way that they perceive will be desirable to the interviewer or to social norms, rather than what they actually believe. This may be a conscious or self-deceptive process. This is a common problem in research where data is collected through participant self-reporting [234]. Regardless of standard explanations provided to participants about the goals of the study, participants will always have their own interpretation of its agenda and that of the interviewer, and will adjust their responses accordingly. One backdrop for this study to consider is the general movement towards evidence-based medicine in the case-study countries that may have led to a desirability for alignment with this paradigm. It is also possible that participants gave responses that they believed may further their professional development e.g. by gaining collaborations or capacity building support.

Although not possible to eliminate the risks of social desirability bias, certain techniques can be used to mitigate its influence. These mostly involve being sensitive to the potential for social desirability bias and how this may be manifested during data collection and analysis. Relevant to the methods used in this study are: considering possible drivers of social desirability caused by the researcher, study design and context; the use of neutral and non-judgmental questioning; posing questions that permit respondents to talk about “people in general” rather than directly referring to themselves; exploring apparently normative or appeasing statements; emphasizing that participation would lead to no direct benefits; and triangulating responses with other data sources [234 ,235]. All of these techniques were incorporated into the participant interviewing and analysis methods. Using observational methods is also helpful for understanding how participants actually behave, rather than how they say they behave. However, observational methods require a lot of time to be spent on a single case, and therefore were not possible to conduct in this study due to the aforementioned trade-off between depth and breadth. To compensate for this, a follow up study will be conducted that explores trial issues in more depth by limiting research to a single “trial case” and using observational methods. This is addressed further in the final discussion chapter (section 7.5 page 352).

Positivists may be concerned by the subjectivity inherent in the qualitative study design, particularly the flexibility, purposive sampling and bias in data interpretation that may impact on the “validity”, “reliability” and “generalisability” of the findings [218]. However, this thesis takes a relativist approach which cannot be judged by

the same standards as positivist research because it is premised on the “understanding that there are multiple realities, reflecting actors’ different understandings of common experiences” [226]. Failure to appreciate these epistemological differences leads to “a clash of knowledge paradigms” [226].

Regarding concerns over purposive sampling and its impact on generalisability to the wider research community, the aim of this research was not to draw conclusions that were statistically generalizable. Rather, the main objectives were to develop an in-depth understanding of clinical trial contexts and develop analytical conclusions and explanatory conceptual frameworks which could be tested in other contexts and used to develop recommendations [218]. This was facilitated by purposive sampling, because although derived from a limited number of experiences, a diverse range of professional experiences that could provide detailed knowledge on specialist issues were captured. Furthermore, only a few individuals had expert knowledge of certain aspects of trial operations, so random-sampling may have missed these critical participants and only identified common knowledge, producing generic advice.

Regarding validity and reliability, these are constructs relating to quality of positivist research. In qualitative (relativist) research, quality is more defined by rigour in the conduct of research and the analysis and presentation of findings [226], and a thorough understanding and enactment of “best” qualitative research practices [227]. There are a number of different interpretations of what defines rigorous and “best practice” qualitative research [227], but one key hallmark is building “trustworthiness” by being transparent about the research processes

leading to the interpretation of the findings [226]. Guidelines to achieve this have been produced [236] and they were closely followed, where applicable. Key “quality” components incorporated in this study were: clearly presenting the research methods; attempting to reduce researcher and participant bias (mentioned above); attempting to reach data saturation; making analytical and interpretive processes systematic and clear; exploring contradictory contributions and undertaking littoral and theoretical replication of case-studies; and triangulating my interpretations with expert local opinion, participant feedback and detailed comparison to wider literature.

Another key hallmark of quality qualitative research is that of reflexivity. Reflexivity is the process by which a researcher continually questions how their research questions and interpretations are emerging. In particular, there is a need to be keenly aware of how the research process and the researcher’s own construction of knowledge influences the study findings [237]. As such, a researcher needs to consider their selection of participants, their relationship with participants, the questions asked, and the value placed on different types of data during the analysis process. Reflexive practice does not eliminate subjectivity, but rather seeks to highlight and acknowledge the interconnected nature of the research process with the conclusions drawn [235]. Essentially, one is trying to alert themselves to what they consider to be “common-sense”, to question this mind-set, and thereby open up to alternative interpretations.

In this study, my reflexive practice involved receiving training in good qualitative research practice, developing an appreciation for the complexities of social science

research, and incorporating principles of good qualitative research practice into the research design. Secondly, I familiarised myself with the research topic and study contexts, ensuring that the questions posed were relevant, and that the research findings were situated within their context so that the interaction between context and results could be fully appreciated. Having local collaborators who had intimate knowledge of the research context was important for achieving this; the local collaborators were involved in every stage of the research, contributing to research design, fieldwork, analysis and interpretation. Thirdly, it is important to also maintain an “outsiders” perspective, so that there is a critical distance from the phenomenon being studied. This critical distance is needed so that commonly accepted values and norms within a given context can be separated from “facts”. This was achieved by repeatedly investigating the research topic in diverse environments that I was unfamiliar with, comparatively analysing these environments, and questioning the influence of the environment on locally-led trial conduct. Lastly, I kept electronic notes and diaries of my thoughts and experiences during the design, data collection, and analysis phases. This process of writing down reflexive considerations is thought to help facilitate reflexive thinking and ensure subjectivity is highlighted and accommodated [237].

PART III: CASE-STUDY RESULTS

Chapter 4: Understanding the investigators: barriers and enablers to locally-led clinical trials in Ethiopia

“We don’t have the evidence to change local practices, but we definitely know some written guidelines don’t work. There are a number of unanswered questions for trials but we don’t know how to do them.” - FGD3. PPT.1 Physician and trial investigator, Ethiopia, 2011

4.1 Publication

An abbreviated form of this chapter was published in BMJ Open [238]. A copy of this publication can be found in the appendix (page XXXiX)

4.2 Introduction

Given the lack of empirical evidence specifically addressing the barriers and enablers to locally-led clinical trial research in LAMICs, it was decided that a pilot study should be conducted before embarking on full-scale research. This would permit identification of important issues to follow up in subsequent larger scale

research and the testing and iterative improvement of the study methods. Early experience of the research procedures and fieldwork would also give an indication of timelines for future expanded research.

4.2.1 Objectives

The objectives of this pilot study were threefold;

1. To identify, understand and explain the barriers and enablers to trial conduct in Ethiopia, paying particular attention to locally-led clinical trials, and thereby develop an early theoretical framework to inform future expanded research
2. To assess feasibility of fieldwork, including logistics such as study recruitment and methods, to ensure elicitation of accounts of sufficient detail and utility for the study
3. To assess whether those involved in carrying out clinical trials in a low resource setting consider the topic of this research to be appropriate, important and useful

4.3 Study setting

The country chosen for this pilot case-study was Ethiopia, please see section 3.3.1 of the methods chapter on page 84 for further details. According to a review of the Ethiopian national health research system, most research in Ethiopia is conducted by Ethiopia's three main universities' medical and public health faculties. These are Addis Ababa University, Jimma University and Gondar University. Other important conduits of research include 2 dedicated research sites external to the

teaching system and various ministry departments. NGOs and UN agencies also commission, support or undertake research [155].

Research exercises in this pilot study took place in Addis Ababa and Gondar, in March and April 2011. These sites were chosen because they represent 2 out of the 3 major research locations in Ethiopia. Jimma was not included due to the logistical and time constraints of the pilot research. Figure 4.1 shows these locations on a map of Ethiopia. For further details on the study setting, please see section 4.4.2 of the results (page 121).



Figure 4-1 Map of Ethiopia showing Addis Ababa, Gondar and Jimma . Source Google Maps 2014 [239].

4.4 Results

4.4.1 Study population

Two focus group discussions, 1 process mapping exercise and 5 interviews were conducted in Addis Ababa, and 1 focus group discussion and 1 interview were conducted in Gondar. A total of 20 researchers participated; 7 were based at a research centre, 1 at an NGO that conducted research, 2 at a central hospital, 6 at a regional hospital, 3 at a university public health department and 1 at a university pre-clinical research department. Participants had varied job roles. Those currently working on a clinical trial included: senior investigators (n=2), trial managers and coordinators (n=5), laboratory personnel (n=5), and research nurses (n=2). Six medical researchers not currently working on a clinical trial were also recruited, 3 of whom had previous trial experience and 3 did not. In addition to these primary job roles, most participants had multiple professional responsibilities and diverse experience. The professional experience domains covered by the 20 participants are shown in figure 4.2.

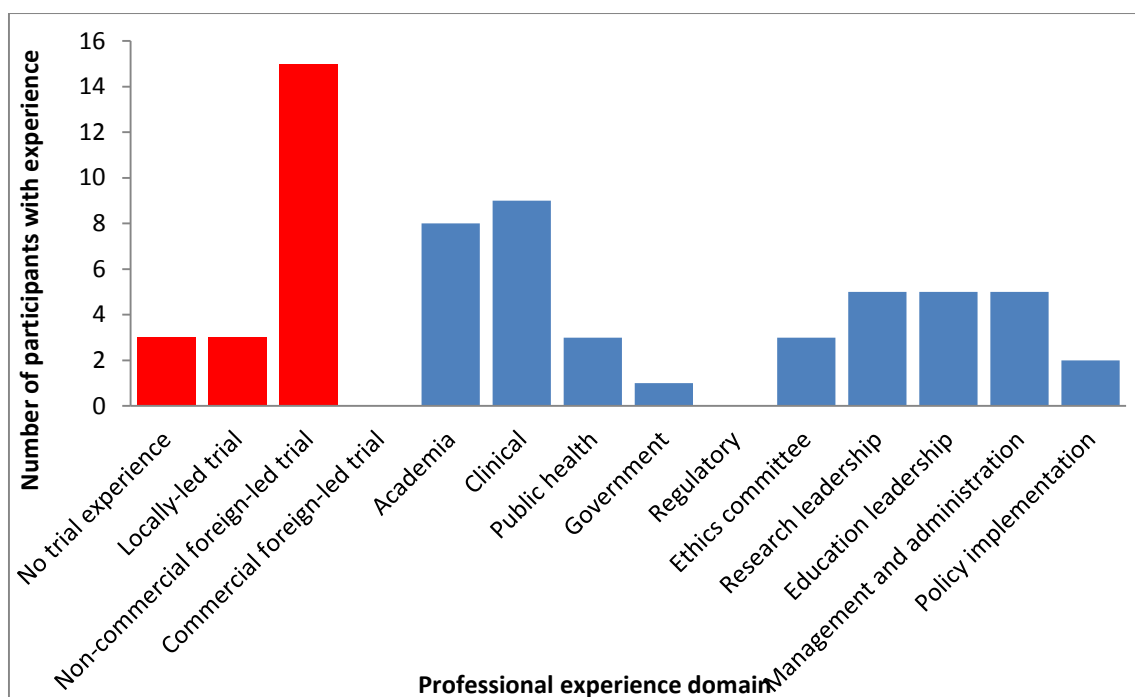


Figure 4-2 Professional experience domains of participants in the Ethiopian case-study. Red bars show trial experience and blue bars show other professional experience domains. Experience domains are not mutually exclusive.

4.4.2 Research setting and context

Most respondents reported that a reasonable amount of health research was conducted in Ethiopia, but despite this there was not a vibrant research community and there was a general lack of research culture in research institutions. Most research was reportedly pre-clinical, descriptive research using case studies or cross sectional analysis.

Participants stated that there were few clinical trials done in Ethiopia, and that the vast majority of those conducted were led by foreign non-commercial organisations. These were split between two types of research models: *long-term trial partnerships* and *short-term trial collaborations*. *Locally-led trials* were reportedly very rare, and some participants were unaware that any had been

conducted. No participants knew of any *commercial trials* that had been conducted in Ethiopia. There are no commonly accepted definitions that delineate between most of these trial types, so for the purpose of this thesis the definitions shown in box 4.1 will be consistently used.

Box 4-1 Definitions of trial types

Long-term trial collaborations:

Non-commercial foreign-led trials where the international partner maintains overall ownership of the project. These trials are conducted as part of long-term partnerships not dependent on individual projects. There is usually strong investment in capacity building and most trial operations are conducted in-country with local staff. The inclusion of local leadership is variable but stronger than in short-term collaborations. Similar to partnership models described in the literature synthesis.

Short-term trial collaborations:

Non-commercial foreign-led trials where the international partner designs the study and collaborates with local investigators to help conduct the trial. Collaboration is short-term and project specific. The foreign partner maintains control of the project and often only recruitment and data collection is carried out in-country. There is usually less capacity development, local leadership and inclusion than in long-term partnerships. Similar to vertical research models described in the literature synthesis.

Locally-led trials

Trials where a local investigator designs and initiates the study. There may be foreign collaborators providing funding or support, but the local investigator maintains overall ownership and leadership of the study. Occasionally may be commercial.

Commercial trials:

Commercial trials designed and led by commercial organisations. Local investigators are employed to conduct the trial locally. Usually follow short-term collaboration models.

Clinical trials were reportedly conducted in three types of institutions: dedicated research sites, hospitals and universities. All clinical trials in hospitals were associated with academic departments. Of the clinical trials reported, all trials in dedicated research sites were long-term trial partnerships. Locally-led and short-

term trial collaborations were conducted in hospitals. Only locally-led trials were conducted in universities. All of the reported clinical trials were funded through international grants, reportedly because local funding was insufficient to cover clinical trial costs.

Regarding the topics of clinical trial investigation, few participants had detailed knowledge of this. However 1 participant who had more extensive experience stated that most trials were phase 2 and 3 studies. One phase 1 trial investigating the use of a novel medicinal product had recently been conducted, but this was reportedly the first novel therapeutic trial in the country because these types of studies were previously not allowed by regulatory bodies. With the exception of this study, all clinical trials reported by participants investigated the use of previously approved therapeutics to treat locally-important infectious diseases. To illustrate the conduct of the different types of clinical trials, 3 examples are presented below (boxes 4.2,4.3,4.4).

Box 4-2 Long-term trial partnerships in a dedicated research institute (FGD.1, PM.1)

This research site was located near to an infectious diseases hospital but had its own buildings and resources that were for the sole purpose and use of researchers. It was well-established, having been founded over 40 years ago. Most of the funding for the site came from a bilateral donor and all research was conducted as part of a long-term partnership with organisations in the donor's country. The site was relatively well equipped compared to the other sites, with dedicated laboratories, clinic buildings, administration departments, IT facilities, and had many staff. Most trial tasks were conducted in the institution. Although largely institutionally separate from government facilities, it trained post-graduate students and some staff and operations were shared jointly with the local hospital.

This site had successfully conducted 3 clinical trials of various phases, and future trials were planned with the long-term partners.

Box 4-3 Short-term trial collaborations in hospitals (FGD.3, INT.5)

Two short-term trial collaborations were conducted in this hospital with the same foreign collaborator, but both were individual short-term project-based collaborations.

Although embedded within the hospital site, the foreign partners had built a dedicated building to house the trials and provide in-patient care. Previously there were very limited resources for research and trial participants had initially been housed in a large tent because the clinic building was not completed before the trial began. When the trials finished these facilities were made available for the hospital. This was reportedly only possible because the trial clinic was integrated with the hospital. However, the trial grant and purchasing was managed by the foreign-partner, only a few local trial staff who were part of the trial received training, and only participant recruitment and data collection was carried out in-country. All local trial staff were trained specifically for the trials and all material resources were also bought exclusively for the trials.

With the support of the trial partner, the local PI had recently acquired funding to lead his own clinical trial in collaboration with a European university.

Box 4-4 Locally-led trials in a universities (FGD.2)

Within this public health department, 2 locally-led trials had been conducted by different academics. Both were a result of foreign funders encouraging local investigators and supporting them with funding applications. Although both trials were successfully completed and gained positive results, neither investigator had continued to undertake trials, due to inability to gain further funding independently.

The public health department had resources to conduct less resource-intensive research, but they reportedly lacked resources to conduct clinical trials. As such, additional resources required for the trials had to be provided by the trial grants. Because these trials were institutionally embedded, the grants were reportedly managed by the university, all trial tasks were conducted in the institution and strong inclusion of faculty members was possible.

4.4.3 Evidence needs and demand for clinical trials

The main areas reportedly requiring research were infectious diseases and community and social problems. In particular, participants said that one of the

priority concerns was understanding why preventable diseases were not being effectively controlled in Ethiopia and learning how to adapt internationally proven effective interventions to the local context. This was because many of the internationally endorsed interventions did not appear to be able to control diseases in Ethiopia or were considered inappropriate. However, participants said that international guidelines often had to be adopted without any local tailoring because local evidence was not available. This led them to say that much more local research into these issues was needed. Only one participant said there was a need for new drugs and vaccines. A senior clinician and trial investigator explained this:

“We need clinical research [in disease areas] that has a different effect in Ethiopia, for example HIV and TB. These diseases are similar as to other places but we have had little success [controlling them] here. So why? Where are the mistakes? These sorts of investigations are easy, they would support awareness and fill gaps.” FGD.3.PPT.1

When asked about the need for and importance of clinical trials, all participants felt that clinical trials were important for addressing the aforementioned evidence gaps. This was because clinical trials were seen as producing the highest quality evidence with which to inform policy. Given the many evidence gaps in Ethiopia, all participants said that more clinical trials were needed.

Regarding the types of clinical trials, no participants thought that commercial trials would help solve locally important evidence gaps because interventions for local diseases would not be commercially profitable. Non-commercial foreign-led studies were seen as important for conducting research that was outside the scope of locally-led trials to address, particularly studies trialling novel investigational products. Existing non-commercial studies were generally regarded as providing

useful evidence and several participants said that their topics of investigations were correctly targeted. However there were reportedly still too few of these trials to meet evidence needs. Conversely other participants reported some suspicion of foreign-led trials, saying that they may be interested in testing products that would not benefit local communities and that foreign-led studies did not always understand the local context and sometimes failed to include and listen to local counterparts or disseminate findings. This reportedly meant that some foreign-led trials were not appropriately designed or their evidence was of little use for local policy.

All participants said that locally-led trials were the most suitable trial type for investigating intervention optimisation but too few were conducted and more were needed. This was reportedly because local investigators had the best understanding of local context and needs, which would ensure correct targeting of research and more acceptable trial designs from ethical and community standpoints. A junior clinician with experience of working on a foreign-led trial explained this through his experience:

“Investigator-initiated trials increase evidence, particularly locally relevant evidence. For instance the Leishmania strain in Gondar seems to be a bit different to the other strains because the drug treatment is working better in the other areas. This will prevent mistakes in clinical care”. INT.6.PPT.1

Locally-led trials investigating intervention optimisation were deemed to be feasible because they would be less resource intensive and complex than novel intervention trials. However, all respondents said that international collaboration, or at least funding, would be essential for enabling locally-led trial conduct through providing resources and expertise. Although many researchers said they wanted

to lead their own trials and had important research questions they wanted to answer, they often did not know how to go about doing this, as described by this senior clinician who had worked on a foreign-led trial:

“We don’t have the evidence to change local practices but we definitely know some written guidelines don’t work. There are a number of unanswered questions for trials but we don’t know how to do them.” FGD.3.PPT.1

Additionally, due to their resource constraints and often simpler operations, some participants perceived locally-led trials to be of lower quality than foreign-led trials. There was no pattern in any of these opinions when comparing participant responses by their trial experiences.

4.4.4 Barriers to trial conduct

In Ethiopia, barriers to trial conduct were identified at all levels of the national research system; macro, organisational and individual. The main influential factors identified in this case-study have been summarised into a mechanistic model (figure 4.3). This is intended to illustrate the interconnected nature of the barriers to trial research and how deficiencies at one level can have cascading negative effects. Each of these issues will be addressed in greater detail in the following sections. However, the following paragraph provides a summary.

System level barriers impact on all levels through often dysfunctional regulatory and administrative systems, insufficient funding allocation and limited ethical review capacity. Suffering from limited resources, the organisational level provides limited research learning opportunities, which negatively impacts on human resources for research. These deficiencies, combined with adverse regulatory and administrative

systems, make operating clinical trials difficult. The combined effects of insufficient resources, limited learning opportunities and difficult operations result in a disabling research environment at an individual level. This reduces awareness of trials, limits competence and self-efficacy, and reduces motivation to undertake them. Few trials are attempted and this forms a negative feedback loop by reducing opportunities for experience.

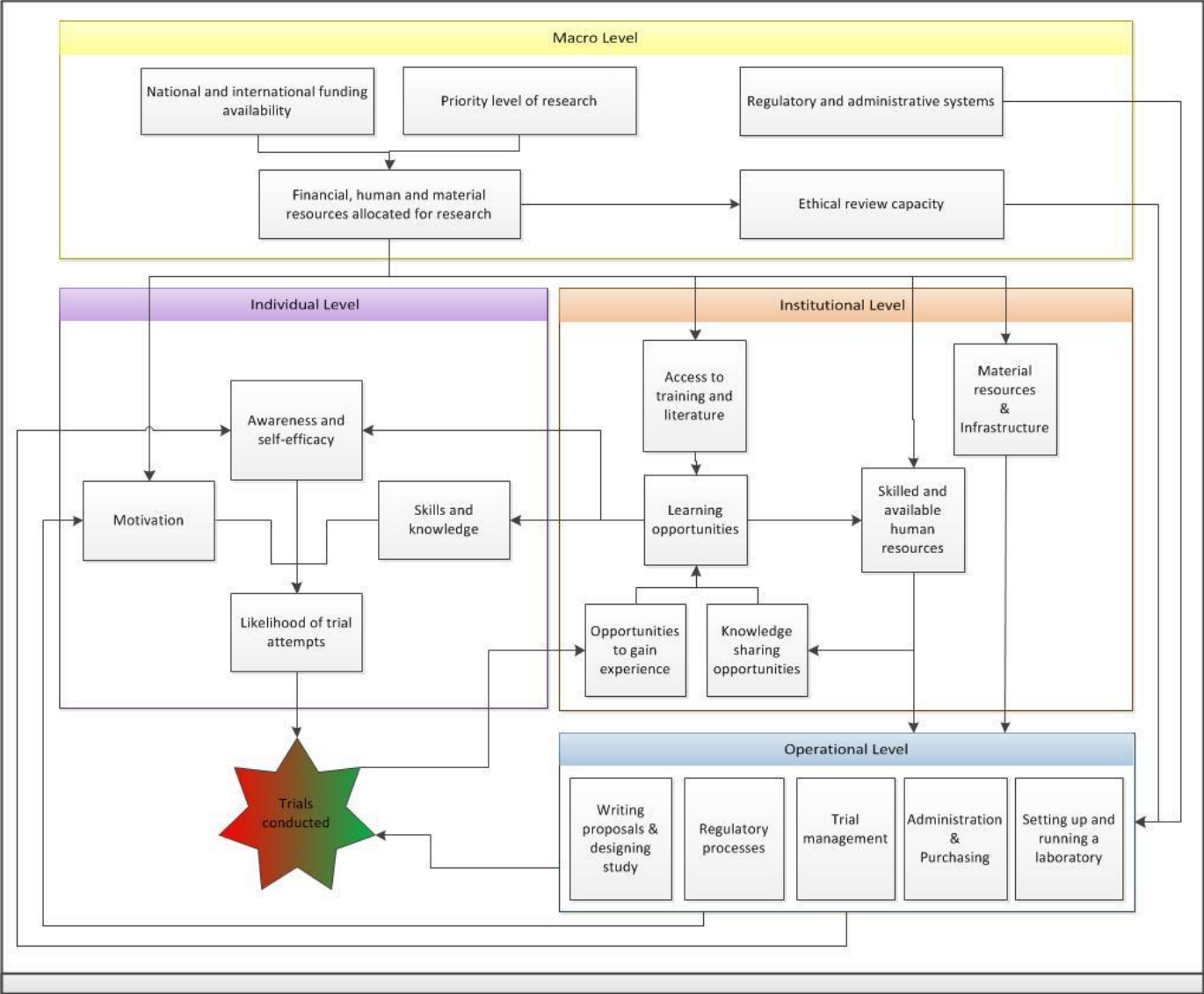


Figure 4-3 Mechanistic model of the influences of the Ethiopian research system on trial undertaking

4.4.4.1 Financial resources for clinical trials

Lack of funding for trials was reported by almost all participants as one of the most important barriers to locally-led trial conduct. This was reportedly because, given economic constraints and research being considered a low priority by government decision-makers, there was little local funding was available. One participant said that research grants were often limited to \$1500 USD. As such, all clinical trials reported in this study were internationally funded. However, many participants said that international grants were highly competitive and applications rarely succeeded. A few participants felt that part of the problem was that international funders did not consider Ethiopian researchers to be credible. Others said that most local researchers did not have the knowledge and skills to write quality grant applications, and some found the process so difficult and off-putting they often did not bother. However, aside from difficulties gaining international funding, only one participant (junior trial investigator) was concerned that clinical trials were exclusively supported by foreign nations. However, he said he lacked the knowledge and skills to advocate for greater national and institutional attention to clinical trials.

To increase the likelihood of gaining international grants, many participants said that support and guidance was needed and most considered international collaboration to be essential. Indeed all the participants that successfully gained international grants to conduct trials were supported by international collaborators or outreach activities of funding agencies. This difficulty accessing international funding and low investment by local government reportedly resulted in few

resources for research that restricted the scope of trials that could be attempted. Furthermore, although local funding was restricted to specific government priority areas, one researcher who was previously a senior government decision-maker (INT-1, PPT-1), said that research still lacked strategic focus and this fragmented research into piecemeal efforts that were of limited use for policy. However, it was unclear if this was due to a failure of national government to focus research or international funding to harmonise with local priorities.

4.4.4.2 Regulatory and governance bottlenecks

All respondents reported that complex and strict government regulations made it very difficult to investigate novel interventions and recruit vulnerable populations. Research into these topics was apparently possible but would require a great deal of time and effort to justify it. Regulatory and ethical review times also introduced delays and it was not uncommon for grants to expire before all approvals were in place. However, studies investigating approved interventions or those considered minimal risk were usually not problematic. A trial PI explained the problems with regulatory and ethical review:

“They have no clear guidelines so it is problematic getting approvals. They are also not experienced enough and so are overcautious and they cannot decide on interpretations”.

FGD.1.PPT.1

Ethics committee members who contributed to this study admitted that limited resources, knowledge gaps and membership shortages slowed review times, but also pointed out that poor quality applications meant re-submission was regularly required. They emphasised that clarification of regulations and developing review

capacity were essential to facilitate trial implementation and that more training in research ethics for both reviewers and researchers was needed. One participant explained that The Ethiopian Bioethics Initiative is already working towards this. Funded by the European and Developing Countries Clinical Trial Partnership, this initiative helps research sites to form institutional review boards (IRBs) and train committee members on principles of ethical clearance. Under this grant they have established and trained 11 IRBs.

4.4.4.3 Administrative bottlenecks

University, hospital and government administration systems were near-unanimously regarded as bureaucratic, overly-complicated and blamed for many operational delays. This reportedly meant that multiple approvals and signatures were needed for research permissions. Furthermore, obtaining these signatures could reportedly take weeks or months and required a lot of “nagging” because research was not seen as a priority and decision-makers could be suspicious of research.

Purchasing supplies for clinical trials was the most commonly reported problem because most procurement applications had to go through an approval committee. This was apparently implemented to reduce corruption and the depletion of foreign currency reserves needed to make international purchases. However, this procurement process was very slow often taking up to several months for simple laboratory supplies such as antibodies.

Local research support services were not available to any participants except those in dedicated research institutions, so all research budgeting and administration applications had to be done by the principal investigator. This reportedly took up lots of time and failure to complete budget reports could result in penalisation. However, the dedicated research sites in this study also had to purchase products through local systems, and even with their own administrators this was problematic. The only participants who did not find purchasing a problem worked on foreign-led trial where the grant and purchasing was managed by the foreign partner.

To cope with these administration problems, many investigators said they required an administrative assistant but could not afford one. The director of research at a hospital said he had considered asking foreign collaborators to manage his grants in an effort to bypass these bottlenecks, but was put off from doing so because collaborating institutions would claim a substantial part of the grant in overhead costs:

“The university finance department is a bottleneck. You really need an admin assistant to help with this. Most doctors do not want to go through the pain of organising and administering all this. Also if you do not report your annual budget on time you may be penalised and have your salary suspended. The clinical trial financing really increases the amount of work you must do for your budget reporting. If I got a good grant I would hire an admin or research student to manage these issues. Another possibility is to put the grant in the hands of the collaborating institution and get them to purchase items for you. But they request 30-40% of your grant to in return for administration and using their name. The local university charge is only 10%.” **INT.3.PPT.1**

4.4.4.4 *Material, infrastructure and knowledge resources*

Participants reported that a general lack of research materials and infrastructure in universities and hospitals reduced the number and scope of trials that could be conducted. Quality laboratory facilities were in particularly short supply, with both advanced and basic equipment such as freezers sometimes lacking. As such, most resources for clinical trials had to be provided by project grants, but because funding was limited or difficult to obtain, this institutional capacity development was rare. Dedicated research sites were better resourced due to long running international support, but still reported material capacity constraints.

Although foreign-led trials developed material research capacity that was of benefit to the wider institution, the project-specific or thematic nature of this capacity development meant that even dedicated research sites reportedly lacked capacity to be able to conduct a broader range of research. A researcher in a dedicated research institute that had conducted a number of foreign-led trials explained this problem:

“We have a freezer full of important samples that need to be analysed, but we have no specific funding or resources for that. So they just stay in the freezer. We also need guidance on how to do this”. FGD.1.PPT.7

Locally-led trials also developed institutional material capacity. However, the general opinion was that because their budgets were much more constrained than foreign-led trials, they were less able to invest in material capacity.

Access to knowledge resources was commonly reported as problematic by university and hospital employees, but not by staff working in dedicated research

institutes. Poor library facilities and access to computers and the internet were the most common complaints. When internet access was available, the connection was slow and intermittent. However, there were conflicting opinions over access to online journals. Several respondents said they had sufficient access through HINARI and other similar initiatives that negotiate free journal access for LAMICs. However, other respondents said they only had access to abstracts and prominent journals were not available. It was suggested that this was because HINARI was only useful for certain journals and institutional access frequently changed. This reportedly meant that it was difficult to learn about research and clinical trials, information was not available to plan research and write grant applications and publications, and local researchers became isolated from progress in their fields.

4.4.4.5 Human resources for clinical trials

All participants, regardless of their profession or institutional affiliation considered human resources to be one of the most severe barriers to clinical trial conduct. Respondents stated that there were too few investigators with the technical expertise to initiate a trial and there was also a shortage of skilled research staff, with one investigator on a foreign-led study stating that if one or two staff left, their trial could not continue.

This lack of expertise and research skills was blamed on minimal research focus in education, a dependence on theoretical teaching rather than practical learning, few knowledge resources, few opportunities to gain experience because trials were rare, and few opportunities for knowledge sharing because there were so few local

experts to provide mentorship. The lack of attention to teaching and training research was most problematic for clinicians because hospitals and medical schools in Ethiopia reportedly lacked a research culture and evidence-based medicine was not always valued. A trial clinician working on a foreign-led trial explained this:

“From my undergraduate experience, I was trained to be a clinician and not a researcher; this is from a curriculum point of view. Few clinicians use clinical trials as they are involved in primary care and not research. They have no spare time to think about research...We need the opportunity to have a simple role and experience to get more people to do more trials. As more people get involved in simple research and trials, more research will be done”. **INT.6.PPT.1**

Key problematic skills gaps reported by participants included: designing clinical trials, writing proposals and funding applications, data management and statistics, laboratory skills and good research practices e.g. GCP, and publishing research evidence. To overcome these skills gaps, participants said research needed greater emphasis in education and students should be encouraged to do research after they graduate.

However, as alluded to by the above participant, individuals skilled in trials were often too busy with regular duties to be able to conduct research. Most senior trial staff were clinicians, and while release from routine duties to research could be negotiated (up to 30% of their time), they complained that healthcare tasks still had to be prioritised. Academics officially had greater time to be spent on research but this was regularly cited as insufficient or not practically made available because teaching and administration took up most of their time. Furthermore, skilled individuals, particularly clinicians, were reportedly not motivated to conduct or work

on research due to poor incentives. This is discussed in more detail in the following section.

Even foreign-led trials in hospitals or dedicated research units reportedly suffered from these manpower shortages, either because it was difficult to find skilled staff, funds were not available to incentivise staff recruitment, or because their clinical staff were jointly employed by the Ministry of Health and only part-time secondment for research was allowed. A PI in a dedicated research unit explained this:

“To be able to progress quickly with research, we really need to be permitted to employ full-time staff and pay them properly. This would be the magic formula!” FGD.1.PPT.2

4.4.4.6 Awareness, motivation, and self-efficacy

Although lack of trial knowledge and skills were barriers to clinical trial conduct, other issues at the individual level also reduced the availability of human resources to undertake or work on trials.

Participants reported that limited awareness and understanding of trials among their colleagues reduced interest in conducting or working on them. This was reportedly because without awareness, people did not think about trials, did not consider that they could answer research questions themselves, or were not motivated to get involved because they did not understand the potential benefits of trials and research evidence. A clinician explained this:

“People do not have the vision that clinical trials will improve patient care because they do not see it in their daily lives. Clinical trials are important but essentially people do not see them enough to think of them”. INT.4.PPT.1

This lack of awareness was blamed on limited emphasis of research and evidence-based medicine during studies and continuing practice, and the rarity of trials meaning few people had the opportunity to see them conducted, get involved, and share experience. Lack of awareness was reportedly most severe among clinicians because research and evidence-based medicine was given little attention in hospitals and medical curricula. Indeed, most of the participants in this study who were involved in clinical trial research appeared to have received their exposure to trials through being opportunistically employed by foreign-led studies or encouraged by international collaborators or funders. This lack of local exposure to trials and subsequent limited trial conduct reportedly resulted in a negative feedback loop:

“The scope of activities is narrowed by the time and economic constraints and the fact few individuals can be involved. Because the scope is narrowed this results in a cycle of fewer people being involved, which in turn results in less motivation, fewer trials and less exposure and realising the way of thinking and less achievement. Then less people are involved and there are fewer trials”. **INT.6.PPT.1 Trial clinician**

In addition to the limited appreciation for evidence-based medicine, poor incentives for conducting research reportedly reduced motivation to get involved in trials and research more generally. Poor salaries, lack of time for research, and limited recognition for research efforts in career progression were particularly strong disincentives. This was because although conducting and publishing research could result in career recognition and higher status, this could take a very long time and did not practically result in much better pay and working conditions than conducting little or no research. As such, many academics reportedly conducted little research and focused on administration and teaching. However, this problem was more acute

for clinicians because they received little or no salaried time for research and promotion could be achieved without any research, so they were better off spending their free time in private practice rather than research. The head of a clinical department who had never conducted trials explained his opinion:

“The problem is that this [clinical trial research] will take lots of your time and while it is possible to reduce your clinic hours, this means you would lose money. The country does not pay you even though it is for public benefit. There is no incentive, in short”. **INT.4.PPT.1**
Senior clinician

Overall these poor working conditions and rewards for research were said to discourage students from entering into research after studies or caused them to migrate overseas to pursue research careers. Research leader respondents said that to increase motivation, the potential benefits of clinical trials for the population should be emphasised through awareness activities, and research should be more institutionally required or rewarded with small financial incentives. For participants who had conducted trials despite few incentives, desire to improve patient care was an important motivator. However, they were also reportedly motivated by learning and developing themselves professionally, and the potential for travel and collaboration opportunities.

However, even if individuals had the awareness and motivation to conduct trials, respondents said that most researchers were not confident enough to lead one. This lack of confidence was reported to be caused by perceptions of complicated or “impossible” operations creating a “phobia” of trial research. Such perceptions were reportedly exaggerated, since locally-led trials were considered feasible by trial experienced participants, but were propagated by lack of exposure to trial research

and successful role-models. To overcome this “phobia”, trial experienced participants suggested that people needed an opportunity to see and take part in research and trials. A junior trial investigator on a foreign-led trial explained this:

“We need to develop and support a research culture. We need grants for beginner researchers to do research and get practice - this would take away the phobia. When the phobia has gone there will be floods of research. We need to open our eyes and see what can be done...Even small research will be an eye opener and the phobia will be gone.”

FGD.3.PPT.2

However, it appeared that more than just experience of trials is needed because even some senior investigators on foreign-led studies apparently still felt unable to lead their own trial. Therefore, for these individuals, it appeared that the problem was more a lack of self-efficacy. The local director of a dedicated research institute said that this situation meant local investigators became dependent on foreign collaborations approaching them and failed to take initiative for leading research:

“We need to encourage people to see that they can do research, so they do not just wait for foreigners with big grants, but take initiative and responsibility for the local health problems. The new generation is better, but the old generation is set in their ways and dependent on foreigners initiating interest.” **FGD.1.PPT.1**

4.4.5 Trial operations and management

The system-wide barriers to trial conduct mentioned in the above sections reportedly caused serious operational difficulties during the start-up stage of trial conduct. However, once intervention delivery began, there were few major challenges. For locally-led trials, planning and funding was reportedly most difficult, but once these operations were completed, they faced similar challenges to foreign-led trials. The exception to this was a short-term trial collaboration that appeared to encounter few problems. However this was probably because most operations were

conducted in the collaborators home institution. The main operational hurdles and their reported causes are summarised in table 4.1.

Table 4-1 Participant reported operational hurdles and their causes

Operational Hurdles	Reported causes
1. Difficulty writing proposals, and gaining funding	• Little local funding, competitive international funding • Technical ability and confidence lacking • Unsure of funding process; investigators don't complete application • Lack of training
2. Slow regulatory and ethical approvals	• Complex and unclear guidelines • Limited ethical review capacity • Poor quality submissions
3. Problems with trial management	• Difficulty coordinating stakeholders • Poor communication between partners due to lack of trust • Limited attention to staff development • Poor planning
4. Burdensome administration	• Complex and slow administrative systems • No administrative support • Slow purchasing systems
5. Problems with setting up and running laboratory tests	• Limited funds and facilities • Slow product delivery • Lack knowledge in technologically advanced procedures • Lack of normal ranges and baseline parameters • Difficulties maintaining equipment

To more concretely demonstrate how system-wide barriers can impact on a trial's operations, data from the process mapping exercise of a trial conducted as part of a long-term trial partnership in a dedicated research institute are provided. The narrative from the discussion is summarised in box 4.5, and figures 4.4 and 4.5 show a tidied version of the process map drawn.

Box 4-5 Summary narrative from the process mapping exercise (PM.1.)

Registering the clinical trial caused considerable delays because task allocation was overlooked. Ethical approval for this relatively complex study took 12 months due to a cycle of resubmission. Ordering to delivery of supplies routinely took 3-6 months. Data entry and analysis were delayed because the data management system had not been considered early enough and training could only be obtained in Europe. Some laboratory tests were outsourced to a local private laboratory because staff lacked the training and equipment, while other assays were complicated by lack of normal ranges for local populations.

Laboratory staff said they lacked sufficient training to perform the required laboratory tests because of a lack of formal procedures for learning new skills and techniques and a lack of management attention to their professional development. This also reportedly made them feel undervalued.

In hindsight the PI would have taken more care with planning and preparation and made roles and responsibilities clear from the outset. However, the laboratory staff had still not been trained, even though a new trial was starting shortly.

As can be seen from these figures, the process mapping exercise produced a thorough account of the many processes involved in conducting a clinical trial and identified many of the commonly reported barriers, and the importance of trial management and planning. The participants found the mapping exercise very easy, intuitive and satisfying, and it resulted in a detailed and useful discussion which contributed towards many of the sections presented previously.

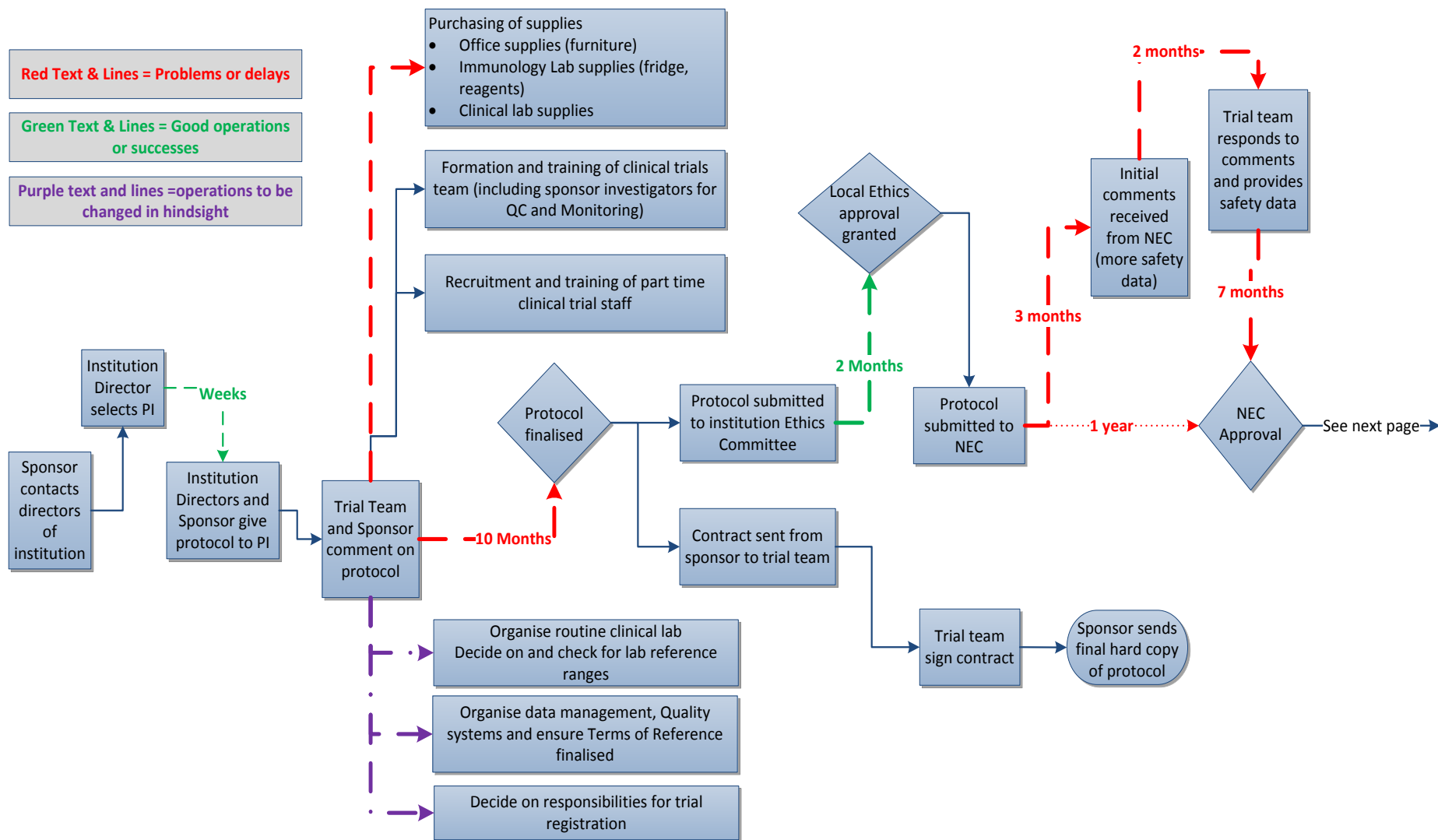


Figure 4-4 First page of the process map of a foreign-led trial (PM.1)

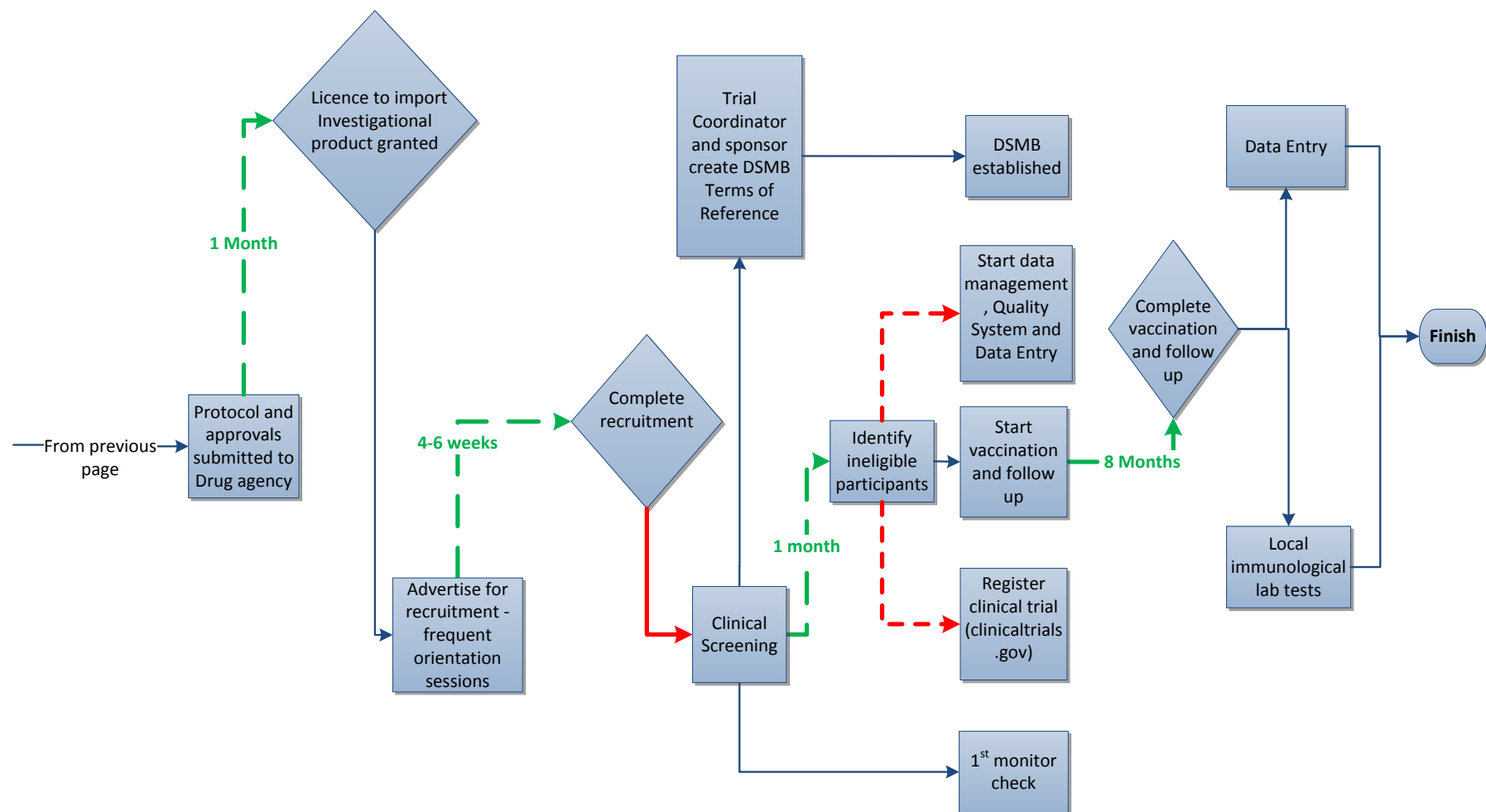


Figure 4-5 Second page of the process map of a foreign-led trial (PM.1)

Although resolution of operational bottlenecks was largely dependent on system-wide capacity improvements, participants from the process mapped long-term partnership trial and a short-term collaboration trial reported that better trial management was needed. In both trials, a lack of coordination and communication between local and international stakeholders reportedly resulted in planning tasks being overlooked and logistical difficulties. In the long-term partnership this was attributed to the foreign partner not understanding local processes and logistical and resource constraints. To overcome this, they suggested that the foreign partner needed to be given a greater understanding of local realities. In the short-term collaboration, the local PI attributed this to the foreign partner failing to listen to and include the local partners because they did not trust them. Apparently it took some time to build up the trusting relationship, but once this was achieved, trial management improved.

In addition to better trial management, participants suggested that keeping trial designs simple and only investigating approved interventions in non-vulnerable populations would avoid operational problems. Indeed, because these trial designs were more associated with locally-led studies, some participants thought that locally-led trials could potentially be operationally easier than typically more complex foreign-led studies.

4.4.6 Developing human resources: Training, knowledge sharing and trial experience

Equal to their value for building knowledge, many participants saw trial and research training, and knowledge sharing as key enablers for increasing awareness, self-efficacy and motivation. Training was viewed as important for awareness, motivation and encouraging staff to consider their workplace challenges in a more enquiring light, and knowledge sharing boosted researcher's confidence that trials were achievable. To be most effective, participants suggested that training and knowledge sharing needed to be provided regularly, so developing sustainable training capacity was important. To increase knowledge sharing, participants thought that mentorship, departmental workshops and seminars on clinical trials should be organised. Many participants also said that training and knowledge sharing would be more effective if grounded in locally relevant examples.

However, opportunities to work on trials were deemed most important for developing human resource capacity because work experience was the only way to develop practical trial skills. Practical experience also reportedly raised professional standards and dispelled what one respondent termed "pseudo-confidence" (INT - 4 PPT -1 - Clinician and trial PI); meaning to continue working in a sub-optimum way because knowledge of more rigorous methods was lacking. Furthermore, trial experience was reportedly most enabling for awareness and self-efficacy and only after gaining practical experience did participants sometimes feel ready to conduct their own trials. Trial experience was also highly motivational because it was prized

for professional development. Although clinical trial experience was most valued, some participants suggested that any research experience would be helpful.

Problematically, all these learning and development opportunities were rarely provided by national institutions, especially hospitals. As such, trial training and skill development was mostly provided through clinical trial conduct. However, trial numbers were very limited and only a few local individuals could usually be involved in each trial. Participants with experience of working on locally-led and short term trial collaborations thought that locally-led trials provided the best learning experience because they would allow greater local staff and institutional inclusion, and more responsibility and ownership of trial processes. They also suggested that locally-led trials could allow trial experience rotations, so more local staff could get involved. However, for the staff that could be involved in short-term trial collaborations, there were reportedly excellent technical capacity building opportunities through training in good research practices, GCP and laboratory skills.

Participants working in dedicated research institutes saw little difference between the learning opportunities of foreign and locally-led trials. This is probably because the trials conducted in dedicated research institutes were part of long-term trial partnerships that had strong local inclusion in most tasks, employed a lot of local staff and helped train post-graduate students.

Given the scarcity of trial opportunities in Ethiopia, some participants suggested that national or international experience exchange programmes would be useful. A senior clinician explained this through her experience of working on a short-term trial collaboration:

“What we really want is for a south-south collaboration like Kenya or Uganda to do exchange placements for our junior staff. This would show people in resource-limited settings it is possible to do trials and would motivate people much more than website or e-learning.....She [referring to research nurse] has been to Kenya and Switzerland and this has helped her to see how clinical trials are done and what is good and bad and see the possibilities. ” FGD.3.PPT.1

4.4.7 The importance of collaboration and networking

While some respondents articulated that foreign-led trials had downsides and many said they would prefer to lead their own trials, most participants were very positive about international collaboration. This was because given local capacity and financial constraints, for locally-led studies to be operationalised international funding and support was essential. However many participants emphasised that there was a need to protect local leadership and intellectual independence when collaborating. International collaboration was particularly valued because it helped local investigators to develop protocols and gain international funding through providing technical expertise and credibility. A senior academic and ex-government minister explains the need for locally-led studies but also international collaboration:

“The priority is addressing local concerns like field-based optimisation. Weight should be given to locally initiated ideas. However, you should then ask for international assistance and collaboration. The investigator- initiated trial is all about the idea and not about the operation. You do not have to re-invent the wheel; you should make the most of global knowledge and skills. Everyone should chip in with their appropriate competence and expertise. This way the work will be faster and more efficient and local researchers will have access to technologies”. INT.1.PPT.1

Furthermore, although locally-led trials reportedly had advantages over foreign-led trials, all participants thought that foreign-led trials were also helpful for increasing the evidence-base and developing research capacity through their greater resources and budgets.

However, collaborations did not appear to be able to develop sustainable capacity. This was evidenced by locally-led trials not being repeated without continued foreign support, many investigators with foreign-led trial experience feeling unable to run their own trials, and research sites lacking capacity to conduct broader research portfolios. Furthermore, while several senior investigators had little problem finding collaborators, other participants, especially junior researchers said they lacked contacts and knowledge to develop partnerships and felt isolated from the international research community. To help overcome this, some participants thought that networking tools would be helpful.

Several participants said that local collaboration would be useful for sharing expertise, leveraging resources more efficiently through pooling costs and staff, and may help develop more self-sufficient research capacity. However local collaboration was reportedly very uncommon. This was attributed to researchers' "egos" preventing them from getting along or poor motivation and appreciation for evidence-based medicine preventing interest. Relationships between academics and clinicians appeared particularly bad, as shown by this public health academic's comment:

"There should be a centre for local collaboration, but there is not because of researchers' egos. Also doctors are arrogant and do not give credit to their collaborators, so we don't want to work with them. They are not keen to engage in research because they can make money elsewhere and they are not interested in evidence-based medicine." **FGD.2.PPT.2**

4.5 Discussion

The participants in this case-study felt that locally-led clinical trials would generate highly useful and applicable data, which supports the call for more local

evidence generation in LAMICs. This pilot research successfully identified barriers to the implementation of locally-led trials at all levels of the research system in Ethiopia, and demonstrated the importance of key enablers for breaking down barriers in somewhat unexpected ways. The challenge of how to support more locally-led trials in Ethiopia is now considered.

4.5.1 The Ethiopian research system

A detailed review of the Ethiopian Health Research System agrees with many of the findings of this study on the barriers to clinical trial conduct, including: lack of funding, limited regulatory and ethical review capacity, difficult administration systems, few resources for conducting and learning about research, limited human resource capacity and allocation, and few incentives to conduct research [155]. The mechanistic model of the Ethiopian research system influences on trial undertaking (figure 4.3), presented on page 128, demonstrates how interconnected the research system is, with deficiencies at one level causing barriers and negative feedback loops at another. This empirically supported presentation of the interconnected nature of the research system is novel within the literature. However it is important to emphasise that this description is not universal and individual examples of enabling practices and trial capacity existed within Ethiopia.

4.5.2 Research sustainability and system-wide development

All capacity development appeared dependent on, and attached to, international clinical trial grants and foreign collaborations. This dependency extended to locally-led trials because foreign collaboration was reportedly essential for gaining

international funding and operationalising trials. Therefore, even though locally-led trials were considered feasible, they would not be so without foreign assistance. This was clearly seen in all examples of locally-led trials because they were only achieved through foreign support.

The problem with this situation was that while both locally-led and foreign-led trials and collaborations could develop research capacity and enable research, this did not appear sustainable, as evidenced by locally-led trials not being repeated once foreign collaboration was withdrawn. The thematic focus of capacity development attached to clinical trials meant that broader research capacity to investigate different research topics was not developed. Additionally, even dedicated research institutes with their greater resources still had considerable trouble conducting clinical trials due to system-wide barriers outside of their control. Short-term trial collaborations were better able to cope with these barriers by managing most aspects of the trial in the foreign partner country, but this limited their ability to develop human resources because so few local staff could be employed and opportunities for them to be involved beyond recruitment and data collection were limited.

Therefore, in Ethiopia, it appeared that to develop sustainable capacity to conduct locally-led trials, system-wide capacity development was required. This more comprehensive capacity development beyond projects or individual research groups is unlikely to be possible through capacity development attached to individual trials. However, with the exception of one research director complaining that more local initiative and responsibility was needed to address national health

research, and a junior investigator saying advocacy was needed to encourage national and institutional investment, most participants considered development of research capacity to be beyond national capabilities and therefore the responsibility of foreign development actors to address.

4.5.3 Building an enabling research environment

Regardless of the responsibility for system-wide capacity development, several strategies for developing greater locally-led research capacity in Ethiopia were identified.

Increasing opportunities for research training, knowledge access, knowledge sharing, and trial and research experiences, would reportedly increase human capacity to conduct and work on trials. This could also potentially reverse the reported negative feedback loop of lack of trial expertise leading to lack of knowledge sharing and trial experiences, into a positive feedback loop. This is because as more individuals gain trial expertise and conduct trials there would be more sustainable learning opportunities. As suggested by some participants, one way to maximise the ability of trials to deliver these enablers would be to allow more local researchers to get involved in trials, possibly through experience exchange rotations. Locally-led trials were considered as most feasible for doing this because they were more institutionally embedded and would involve more local staff. However, it also appeared that long-term trial partnerships in dedicated research institutes could also do this. A commissioned report on the human capacity building needs of Ethiopian new public universities agrees with these findings, stating that

to establish a research culture in these universities, greater teaching of research methodologies using more practical techniques, access to publications, and research experience opportunities are needed [220].

There were fewer suggestions for how material capacity could be developed other than by conducting more clinical trials. However, it seemed important that this capacity development should be less thematically focussed to develop capacity to conduct wider research portfolios. Regarding ethical review and regulatory capacity, there was a clear need for training of researchers and reviewers, clarification of guidelines and providing greater resources for review bodies. Encouragingly, the Ethiopian Bioethics Initiative was addressing this. Despite administration being considered a major barrier to trial research, there was little consideration of how the situation could be improved. However, the aforementioned report on strengthening Ethiopian Universities also identified administration as a major barrier to academic efficiency and suggests that more transparent and efficient systems are required. To achieve this greater training for administrators and managers in management information systems and human resource management is suggested [220]. Discussion on translation of evidence into policy was also conspicuously absent given that most participants wanted more local evidence informed policies.

Although the above actions would help provide greater resources for research, it was clear that for more locally-led trials to be conducted, individual level issues needed to be addressed. This was because lack of awareness of trials, little time,

and low motivation and self-efficacy prevented local investigators from attempting to conduct trials.

To encourage more people to think about and want to conduct trials, there needed to be greater awareness of trial methods, including their potential to benefit local populations through evidence-based medicine. To do this, various training, knowledge sharing and learning modalities were suggested. However, in addition to an interest and appreciation for trials, most individuals appeared to need greater motivation to conduct them. Low salaries, combined with limited funding, high teaching burdens, low quality facilities and frustrations with bureaucratic and operational hurdles found in this and another study [29], all served as strong disincentives to research. For clinicians, this lack of incentives was particularly severe because they had very little time allotted for research, research was not important for career progression and they could make more money through private practice or even routine work. Indeed in Ethiopia, clinical academic staff are paid less than public sector physicians [29]. However, even for academics, time for research was inadequate and research progression led to few tangible benefits.

Providing protected time for research, recognising research within careers, and ensuring career development led to tangible rewards should help motivate investigators to undertake trials. However, with the exception of a few individuals who appeared strongly motivated by intrinsic incentives such as helping patients and professional development, salary incentives are also likely to be needed to offset lost revenue from private practice or the extra work burden that research entailed.

Lack of confidence and self-efficacy reduced the number of locally-led trials conducted and generally prevented local researchers taking more responsibility for local research needs. This attitude reportedly meant that local researchers failed to take initiative in leading research and forging collaborations, and instead were dependent on foreign researchers to approach them. Although knowledge, experience and seeing trials successfully conducted should reportedly increase self-efficacy and confidence to conduct locally-led trials, this does not appear to be a full explanation because some investigators who had worked on foreign-led studies still did not feel ready to lead their own trial. The Cameroon case-study, presented in chapter 5, provided further details on how self-efficacy is developed and why some individuals are motivated to conduct trials in spite of limited incentives. Therefore these issues will be revisited in greater detail in the chapter 5 discussion (section 5.5.2 page 221).

Conceptually, these individual level findings are supported by the The ADKAR model for change in business, government and community [240]. Consideration of change management is relevant here because since clinical trials are uncommon, a move towards encouraging trials represents an organisational change. This model argues that for successful change to occur in organisations, change at an individual level is needed. For successful individual level change to occur *Awareness, Desire, Knowledge, Ability and Reinforcement* are needed.

Awareness emphasises that individuals must know more than that a change simply exists. They must also internalise why the change is important. However to

get individuals to support a change, *Desire* is also needed. *Desire* relates to encouraging people to want a change to take place, usually through explaining how the change will benefit them or something they value. As such these concepts closely fit the reported need for awareness of trials and appreciation for their potential to improve healthcare.

Knowledge represents the theoretical and technical know-how to put a change into action. However, the ADKAR model also argues that *Ability* is needed in addition to knowledge. *Ability* is different from *Knowledge* because it encompasses whether an individual also has the time, resources, and intellectual, physical and psychological states to enact a change. These concepts closely match the findings from this study because to be able to conduct trials, researchers needed time, resource availability and self-efficacy (psychological state), in addition to knowledge and skills.

Reinforcement represents anything that strengthens and sustains a change. *Reinforcement* is usually provided through rewards, recognition and appreciation. Freedom from negative consequences from making a change and accountability to encourage continued performance are also important reinforcements. Without reinforcements, change may occur but would not be sustained, because employees revert to old behaviours because their efforts are not valued. This concept of *Reinforcement* closely matches the reported need for motivational incentives to conduct trials such as financial rewards and career recognition. It also encompasses the need to compensate for private salary loss and suggestions that research should be required for clinicians and academics. Furthermore, it not only

helps explain why locally-led trials are rarely conducted, but also why once they are conducted, they are not sustained.

It is important to note that the ADKAR model approaches organisational change from the perspective that a change is desired by the institution, and individuals require support to enact the institutional goal. However, for participants in this study, the reverse was true; most wanted to conduct trials, but their institutions did not support them in this endeavour. Therefore, even if individuals acted as agents of change and attempted to conduct trials, they were often prevented by their institutional structure, or could not continue conducting trials due to lack of support. This means that for the ADKAR model to be applied to the clinical trial situation in Ethiopia, institutional willingness to support change must be considered important components of *Ability* to enact change and *Reinforcement* to continue enacting the change.

4.5.4 Networking and collaboration

International collaboration was key for developing local trial capacity, either through foreign-led trials or by supporting locally-led trials. Although such capacity development did not appear sustainable, it was nevertheless very useful for getting research done. However, most international collaboration was initiated by the international partner, which made local researchers dependent on foreign initiative. While this may partly be attributed to a lack of local initiative in forging collaborations, several participants said they lacked international contacts with whom to collaborate. As such networking tools to help local investigators to find

international partners would be very useful in Ethiopia. This should also help reduce the intellectual isolation reported by participants.

Local collaboration was also considered important because it could increase knowledge sharing, and help share costs and pool resources. It also seems likely that local research networks could support sustainable training models by experts becoming trainers of trainers and developing mentorship programmes linking experts to junior staff. As such local networking and collaboration has the potential to help develop sustainable research capacity. However, poor relationships between researchers reportedly made local collaboration rare. Creation of communities of practice could help to develop these relationships but proven strategies that foster their development are not clearly established [241]. Networking opportunities such as workshops would be useful, but firstly all stakeholders need to be identified and travel, time and cost can be barriers. Further consideration of how local collaboration and networking can be developed is addressed in the chapter 6 discussion (section 6.4.3 page 289). This is because the findings from the Sri Lankan case-study provide further explanatory detail.

4.5.5 Improvements in the Ethiopian research system

Although few participants considered the national government to have the capability or interest to develop local research capacity, this does not appear to be the case. In 2006 The Ethiopian Science and Technology Agency devised strong implementation strategies to support research [242], these were built on in 2012 [243], and the importance of research and developing research capacities is now

central to the Ministry of Health strategy [244]. Furthermore, Jimma University in South West Ethiopia has recently been applauded for pioneering new innovative teaching methods, valuing research within institutional culture and integrating it in career progress [29 ,245]. Meanwhile, The Ethiopian Bioethics Initiative is working hard to strengthen regulatory procedures. However, despite these positive steps forward, it is clear from participant reports that further improvements in clinical trial capacity are required.

4.5.6 Strengths, limitations and further work

This pilot research was successful in achieving its first objective of identifying barriers and enablers to locally-led trial conduct and developing an early theoretical framework. This has pointed towards causative mechanisms, identified important themes for full-scale investigation and suggested potential recommendations. Many of these would have been missed if only extant literature had been used to guide full-scale data capture.

The second objective to test the feasibility of fieldwork was also successful. Fieldwork was completed within an acceptable timeframe (1 month) and recruitment was not problematic. Although the sample size and range of stakeholders was small, and this limited the breadth of perspectives, the study still accessed diverse experiences to uncover issues in a largely unexplored area, while giving a compelling voice to local investigators. The focus groups and interviews were effective at eliciting general responses from participants. However participants sometimes had difficulty linking opinions to specific examples and context. When

the process mapping exercise was used, it resulted in excellent participant recall embedded in context, and also helped capture tacit knowledge.

Nevertheless, there were gaps in participants' knowledge regarding specific issues such as use of evidence for policy and consideration of how administration could be improved. It would also be helpful to illicit the opinions and perspectives of other stakeholders such as regulators and policy-makers. To provide these broader perspectives a wider range of stakeholders with expertise in specific areas were recruited in the following case studies.

Finally, exploration of the third objective showed that participants consider the topic of this research to be appropriate, important and useful, therefore lending support to further research in this area.

Chapter 5: Lessons from the Cameroon research system; exploring the shortage of locally-led clinical trials in sub-Saharan Africa

“We have a saying that ‘the son shows maturity when he picks up his arrow and goes hunting’. It’s an African saying. You know that the son is mature when he picks up his arrow. He doesn’t wait for his father. He doesn’t wait for his uncle. He just goes hunting. This is what I think I have been able to do more with the other [locally-led] trials”. - FGD.3.PPT.1 Investigator on foreign and locally-led trials, Cameroon, 2012

5.1 Publications

Findings arising from this results chapter and those from chapter 4 were presented at The World Health Summit in Berlin in 2013. The abstract from this oral and poster presentation was published in The Lancet [246]. A copy of this publication can be found in the appendix (page XLVIII)

5.2 Introduction

The Ethiopian pilot data produced valuable and novel findings. To expand on these findings and assess if they have transferability to other settings, a larger-scale case-study was conducted in Cameroon. This case-study was similar in design to the Ethiopian case-study but it recruited more participants with diverse specialist

experiences and explored pertinent issues shown to be important in Ethiopia in greater detail. This should both strengthen the results of the Cameroon case-study and may provide support for the Ethiopian case-study findings.

5.2.1 Objectives

1. To identify, understand and explain the barriers and enablers to trial conduct in Cameroon, paying particular attention to locally-led clinical trials
2. To expand on the preliminary theoretical framework developed in Ethiopia by exploring issues in greater detail and ascertaining which barriers and enablers are common among countries with similar clinical trial contexts, and which are distinct.

5.3 Study setting

Cameroon was selected because in common with the Ethiopian context, it has similar clinical trial capacities, research outputs and development status (see section 3.3.2 of the methods chapter, page 88), each of which were considered important backdrops to the ability to carry out investigator-initiated trials, and thereby allow for some comparability between contexts.

Research exercises took place in Cameroon between June and July 2012 (one remote interview conducted via Skype in March 2012). Research was conducted in 3 areas: Yaoundé, Buea and surrounding region including Limbe and Kumba districts, and Bamenda. Yaoundé is the capital city of Cameroon and is in a Francophone region. Buea is the capital town of the Southwest Region of Cameroon which is Anglophone. Bamenda is the capital town of the North West Region of

Cameroon and is also Anglophone. Although all these locations are in the western part of the country, they were selected because they represent a good portion of the dominant and emerging research centres of the country. Figure 5.1 shows a map of Cameroon, and figure 5.2 shows a map of Western Cameroon detailing study locations. For further details of the study setting, please see section 5.4.2 of the results (page 164).

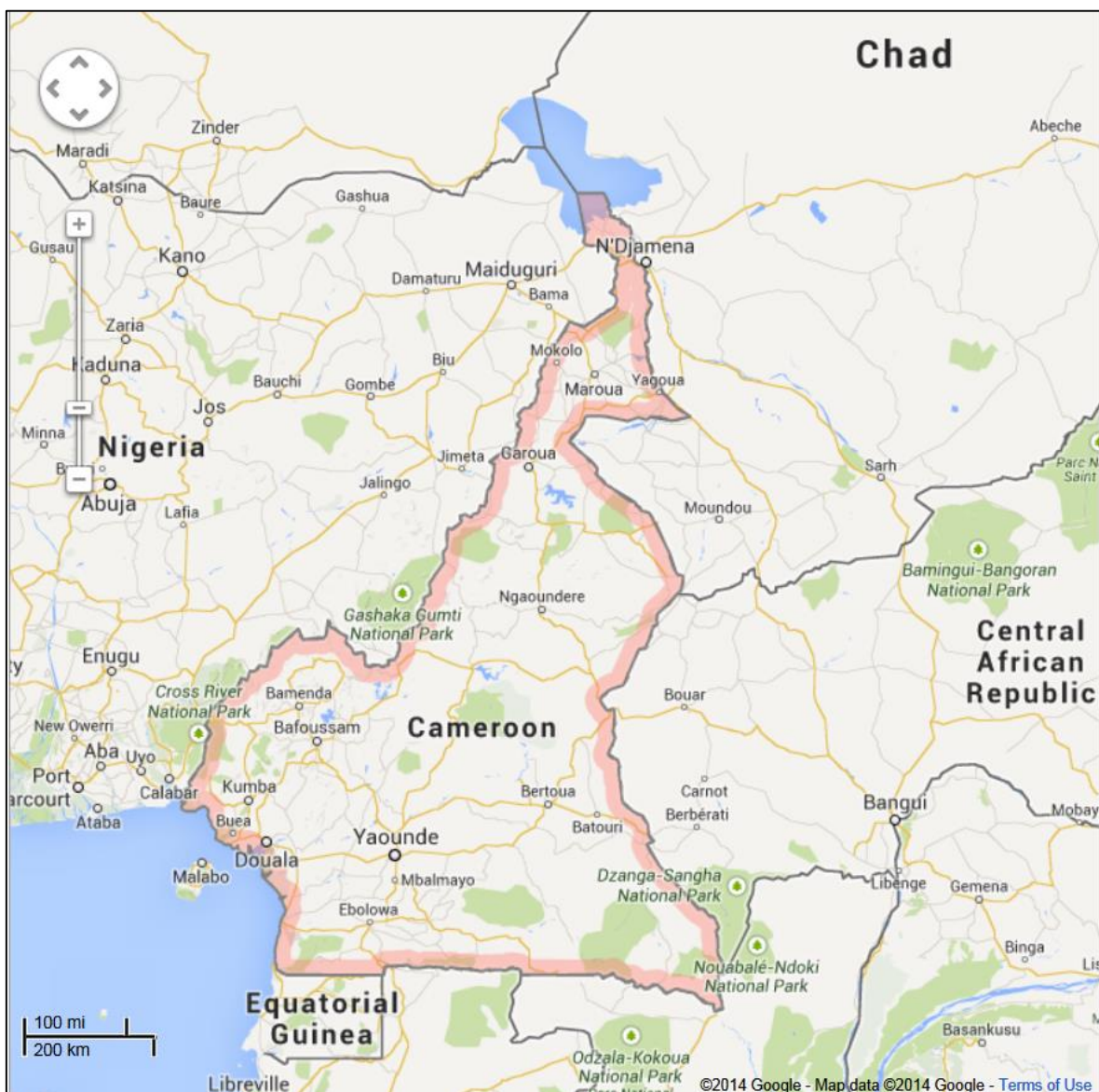


Figure 5-1 Map of Cameroon. Source Google Maps 2014 [239].



Figure 5-2 Map of Cameroon detailing study locations. Source Google Maps 2014 [239].

5.4 Results

5.4.1 Study population

Twenty-eight research exercises with 49 participants were conducted. Participants were recruited from: 3 universities, a medical research institute, 5 hospitals, a provincial community health centre, 2 government ministry of health

departments, an ethics committee, and an NGO. A breakdown of research exercises by type and location is provided in table 5.1.

Table 5-1 Research exercises completed in Cameroon by region

Research Exercise	Regional location			Total
	Yaoundé	Buea including Limbe & Kumba	Bamenda	
Interview	8	6	2	16
Focus group discussion	3	2	1	6
Process mapping	2	3	1	6
Total	13	11	4	28

The participant's primary job roles included: academic (n=7), head of academic department (n=4), academic director (n=2), dean or vice dean of academic faculty (n=4), clinician (n=6), nurse (n=5), clinical department head (n=2), student (n=2) regulator (n=1), public health practitioner (n=1), project manager (n=2), laboratory personnel (n=5), data manager (n=1), data collector (n=2), research administration head (n=1), government ministry department head (n=2), ethics board chair (n=1), and NGO director (n=1). Despite these primary job roles, most participants had multiple professional responsibilities and diverse experience. The professional experience domains covered by the 49 participants are shown in figure 5.3. As can be seen from this figure, the recruited participants combined have expertise and experience of most components of the national health research system.

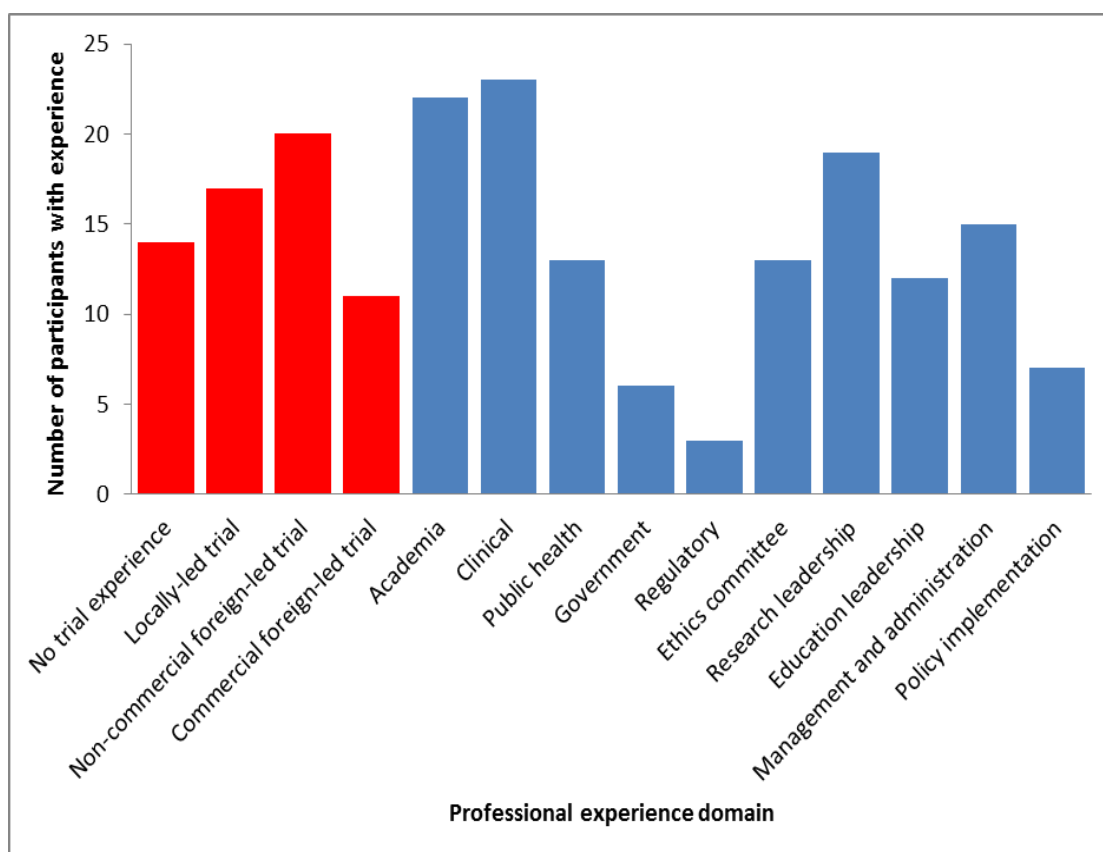


Figure 5-3 Professional experience domains of Cameroon participants.

Experience domains are not mutually exclusive.

5.4.2 Research setting and context

An unpublished review of Cameroon's health research outputs compiled by a participant in this study stated that 70% to 80% of research was pre-clinical and 20-30% clinical. Of the clinical research, most was observational but some was experimental, including a few clinical trials. The lack of experimental research was attributed to inadequate funding and research capacity. Of the clinical trials, participants said that most trials investigated approved drugs, with a few being behavioural studies and novel investigational products. As such, the health research outputs of Cameroon were largely similar to Ethiopia.

The most commonly addressed diseases were HIV, Tuberculosis and Malaria, with less research into Cholera, Onchocerciasis and other parasites, and some non-communicable conditions like cancer and trauma. Research into traditional medicine such as bioactivity of local plants was a growth area of particular academic and commercial interest. However, this research was mostly pre-clinical and participants stated that clinical trials aimed at translating new compounds into medical products were needed.

Like in Ethiopia, the majority of clinical trials in Cameroon were reported to be run by foreign trial groups, with only a small number of locally-led trials being conducted. A few participants reported that government ministries conducted some research, and this was mostly health systems work. Interestingly most foreign-led trials were reported to be commercial studies. However, this perception was not reflected in specific examples provided by participants, as more participants had experience of working on foreign-led non-commercial trials, and most commercial trial experiences were obtained by participants when working abroad in Western countries. Although this could be attributed to recruitment bias, the WHO trials registration portal [59] shows that most clinical trials in Cameroon are foreign-led non-commercial studies. Since the WHO trials registration portal pools clinical trial registration from all other trial registries, including commercial studies, this data is likely to be correct. It is possible that commercial trials were perceived as being more common than they actually were because of the greater, often negative and suspicious discussion that surrounded them. However, regardless of the proportion

that commercial trials represented, they were more common in Cameroon than Ethiopia.

Like in Ethiopia, foreign-led trials were split between short-term trial collaboration models (including commercial trials), and long-term trial partnership models. However, in Cameroon all reported foreign-led trials managed their own grants and administration through structures parallel to national systems. Although locally-led trials had strong local inclusion and were usually institutionally embedded, some local investigators had developed their own research units which were partly separate from the university. The vast majority of funding for locally-led trials came from foreign sources.

Like in Ethiopia, clinical trials were reported to be conducted in dedicated research institutes, universities and hospitals. Dedicated research institutes worked through centres of excellence research models and conducted mostly long-term partnership model trials, and locally-led trials. They were generally institutionally and spatially separate from public research institutions, had the best resources and managed their own administration and grants. While most of these were supported by foreign collaborations and consortia, some were government initiatives.

A mixture of all clinical trials were conducted within universities and hospitals, although short-term trial collaborations were more common in hospitals. Universities had better resources for research than hospitals, but both lacked resources and services to support the conduct of clinical trials. Instead, trials were resourced and supported by individual trial grants obtained by local investigators or supplied through foreign collaborations.

Box 5.1 describes various illustrative examples of how clinical trials were conducted in Cameroon.

Box 5-1 Illustrative examples of clinical trial conduct in Cameroon

Foreign-led non-commercial trials and locally-led trials in a dedicated research institute (PM.5, FGD.6, INT.14, INT.15):

This dedicated research institute was an internationally funded centre that was part of a several disease specific consortia working through a long-term partnership model. It was located several miles from the major university and hospitals of the city. It employed its own full-time staff, and had laboratories, a conference centre, IT facilities and administration departments. Both foreign-led and locally-led trials were mostly funded through the consortia that supported the research institute. Local staff were included in all clinical trial activities, received extensive training, and there was strong local leadership and ownership of studies. Capacity development was a key goal of this research site. Most clinical trials were field-based studies and more were planned.

Short-term collaboration on a non-commercial foreign-led trial in a hospital (PM.3):

This clinical trial was part of a multi-site, multi-country clinical trial. Only the recruitment and data collection were completed in-country. The local collaborators had little training other than an information pack and were provided the supplies for the clinical trial. The hospital had no resources for research, and even lacked stable power and basic equipment to treat their patients. Indeed one of the reported benefits of this trial was that the sponsor had supplied flashlights so that when generators failed, emergency surgical operations could be performed in the dark. To submit case report forms, staff had to use a local internet café. Local staff were compensated though being paid per recruitment, but this reportedly did not cover their personal expenses. This was the only clinical trial in the hospital and no further trials were planned.

Foreign and locally-led clinical trials in a quasi-independent research unit within a university (INT.3):

This research unit was set up by a local university academic to facilitate the conduct of his research. He decided to make his research unit partly separate from the university to allow him to have greater control over his grants, avoid university bottlenecks, and more easily accumulate resources. He had developed the unit over many years through gaining multiple research grants in collaboration with foreign researchers. The unit was housed in a series of buildings accessed through a hole in the university perimeter wall. It contained several laboratories, meeting rooms, insect houses and many university students worked there. The principal investigator had conducted several foreign-led and locally-led trials and more were planned.

5.4.3 Evidence needs and demand for clinical trials

The evidence needs and demand for clinical trials had strong similarities to those reported in Ethiopia. Cameroonian participants reported that the paucity of local experimental evidence meant that few policies were based on contextually appropriate research, and that the majority of clinical guidelines were currently implemented solely based on international recommendations. This was considered problematic because most individuals, including policy-makers, thought that international recommendations needed tailoring to local contexts. The head of a public health NGO summarised the need for this:

“We don’t do enough evaluations of our treatments to see if the medicines that are good in another country are also good in our country. This is a big problem. We need emphasis on applied research to test if international interventions work here and why they are not working well.” INT.16.PPT.1

Clinical trials were highly valued by participants because of the perception that they generated the highest quality evidence that permitted causative conclusions to be made. They were also seen as more reliable, objective, and less biased than observational studies. The head of an academic department explained this:

“So the clinical trial is a step – it is a major step to really see the impact of what it [the intervention] can do. It is to make things tangible, to make things touching the clouds. That is a huge motivation to say that after this process I will know if this drug can help these people better than what existed before. That is a huge motivation. It is really the translation of the research life, research career, that clinical trials bring you”. INT.6.PPT.1

Despite general enthusiasm for most types of clinical trials, many participants were suspicious of foreign commercial drug and vaccine trials and were concerned about misconduct. Citing examples of malpractice, there was a very strong

emphasis on the need to protect patients, as explained by this public health practitioner:

*“We know that they [American drug companies] are taking us like guinea pigs, that the drug is not very good for the subjects and they are coming to trial it on us here and we are wary of that. **PM.2.PPT.1***

Locally-led trials were generally considered more acceptable than foreign-led trials because the investigative topics would be more locally beneficial and local researchers would be more accountable to local communities. This meant that locally-led trials were more applicable to “real life”, as this clinician and PI of a locally-led trial explains:

*“Usually locally initiated trials deal with the real problems of daily life. You see something happening and you want to really understand what is happening. Meanwhile a foreign-led trial may not know the field situation of what you are doing. They do things that they want to do. These things may not necessarily tie with your real problems that you will see in the field. That is where the difference lies. At times, they come with topics that we may find irrelevant.” **FGD.3.PPT.1***

This led many participants to say that more applied locally-led clinical trials were required to better inform local policy. Furthermore, local researchers were considered to be able to forge better relationships with policy makers than foreign researchers, and this could reportedly speed up the policy translation process. However, this argument appeared hypothetical because very few investigators reported that they had influenced policy and most said developing relationships with policy makers was difficult. This issue is addressed in further detail in section 5.4.4.4 (page 181). Additionally, because locally-led clinical trials suffered resource constraints, they were often regarded as inferior to foreign-led studies or less glamorous.

5.4.4 Barriers to trial conduct

Like in the Ethiopian case-study, barriers to locally-led trial undertaking were found throughout the Cameroonian research system. A conceptual model showing the system-wide barriers to trial conduct, the mechanisms that drive them, and their negative downstream effects is shown in figure 5.4. While this figure has strong similarities with the conceptual model presented in the Ethiopian case-study, it provides greater detail and demonstrates directionality of problems through showing the research system from a disabling perspective. It also shows how some issues overlap between system levels, rather than being discretely divided between macro, institutional and individual components. However, it is important to note that the model does not suggest that no examples of enabling practices existed and all problems were universally experienced. Rather it is designed to highlight all the key barriers to locally-led trial conduct reported by participants and how these relate to each other. All of the issues presented in the model will be addressed in greater detail in the following sections.

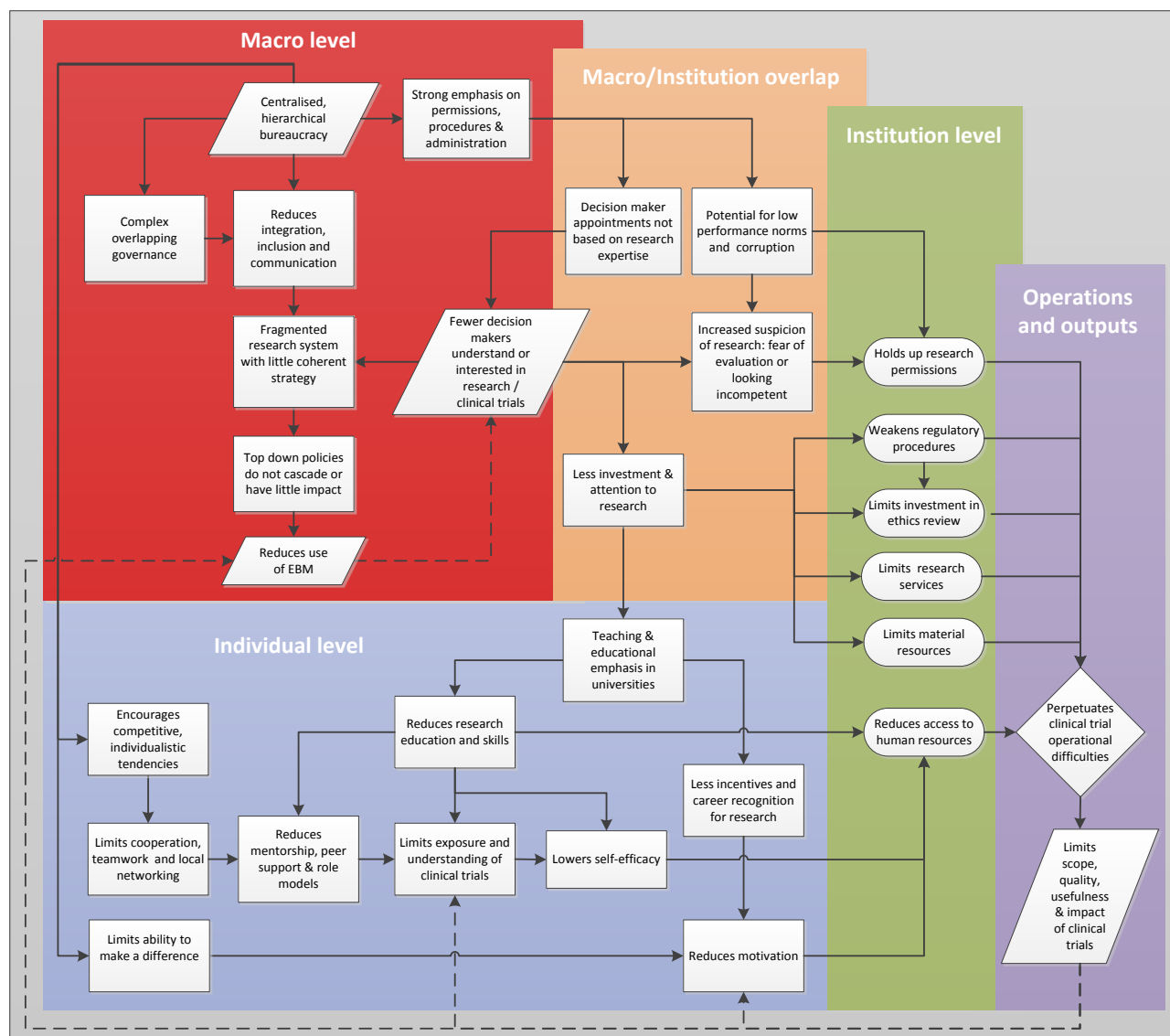


Figure 5-4 Mechanistic model of the influences of the Cameroon research system on locally-led trial undertaking

Note: This model is taken from a disabling perspective and not all barriers may be simultaneously present. Parallelograms represent the start and end of processes. Dashed lines show feedback loops.

5.4.4.1 Research governance and administration

Similar to the situation in Ethiopia, participants unanimously described research governance and administration in Cameroon as bureaucratic and overly complex. However, participants in Cameroon gave much greater detail of the causes and effects of this organisational structure. In Cameroon, this complexity was attributed to top-heavy, hierarchical governance structures designed to maintain central control. This meant multiple administrative permissions were required from each level of governance and strict procedures had to be followed. As such, gaining permissions to conduct research was frequently reported as a slow and laborious affair. This was true for national, regional and district-level bodies as well as universities and hospitals. Within dedicated research institutes, procedures were more streamlined, but because their research frequently required permission from other bodies, they faced similar problems.

Several participants considered these governance issues to be driven by Cameroonian culture, which was reportedly more problematic in Francophone regions. Two illustrative quotes are shown below:

"We must also consider the cultural nature of our society; everything would naturally become complex! FGD.2.PPT.5 Head of academic department (Anglophone)

"In Francophone procedures there is a lot of complications, a lot of administrative bother. You get into a process where, 'Oh, you have to section the person, you need to see this other person, you need to go and see this person. You get this before you see this other person who will now give you authorisation to see this other person.' Basically the procedures are very complex. But it's not the same in Anglo-Saxon areas. It's a bit more simple." PM5.PPT.1 Anglophone PI in working in an Anglophone region.

However, problems with research governance and bureaucracy were actually more frequently reported by participants in Anglophone regions. Therefore, at least for

the participants in this study, bureaucracy appeared generally problematic regardless of the linguistic region.

Several academics stated that jobs in government were highly desirable because of the perceived benefits these positions held. Since ministerial workers were frequently recruited from university administration, participants reported that academics were often more interested in securing administration positions in universities than becoming researchers. Furthermore, because administrative appointments in both universities and hospitals were frequently made for political rather than meritocratic reasons, conducting research and demonstrating excellence was further de-valued, as explained by a senior member of a universities administration:

“We were brought up by a government in which you believe that you can only survive by working with the government. And that has affected the psych of society, believing that if you are not within the government institution then you are not to be fine... The government brought politics into the [university] system in such a way that the lecturers tended to use the university as a place to get a political appointment. And so research was almost neglected because as of that time promotion was based on presidential decree, rather than on research. So with that you realise that most lecturers tend to fight for these positions and give less time to research.” **INT.4.PPT.1 Head of academic department in an Anglophone university**

The reported corollary to this was that administrators in leadership positions in hospitals and universities sometimes had no background in research or medicine, as explained by this public health practitioner working in a district hospital in an Anglophone region:

“So it’s very variable depending on the individual you meet and you might get to certain institutions where the heads are not medical practitioners, they are not researchers, they are purely administrators. So all that you are presenting to them is selling some medical research, it means jargon, it means absolutely no sense. You might go somewhere to look at patients in the hospital and the Medical Officer says the Divisional Officer has to give you

*authorisation. You meet the Divisional Officer and he's purely administrative and he really doesn't give a damn and he wouldn't know! **PM.2.PPT.1***

When decision-makers did not understand research they were reported to often be threatened by it because they saw research as an assessment of their performance. This made it very hard to encourage decision-makers to support research in terms of resource allocation and some may deliberately withhold permissions to undermine research activities, as explained by this clinical trial co-investigator from a Francophone region:

*"If you go to smaller hospitals to look at patients there, then you will need the permission of the District Medical Officer and the Chief Medical Officer. It starts becoming difficult; some will categorically refuse, others ask for documentation or papers that really don't make sense. The long run being that ultimately they are just trying to block you. The duration of these obstacles vary, some people might block you for a few weeks, some might block you for months, for some you might never even be able to recruit patients in their environment." **PM.4.PPT.1***

Other respondents blamed ineffectual administration of research on a widespread culture in public institutions of doing the minimum, and staff only fulfilling their procedural role if personal benefit was possible; "benefit " or "motivation" being commonly used terms to describe giving unofficial favours such as money or hiring friends or family members. Many respondents said this caused problems because if "benefits" were not given, administrators would either hold up processes until benefits were received or do work in a substandard manner. This attitude was reportedly more severe with international research because of the perception that lots of money would be involved and all staff deserved a share. Once again, these attitudes were seen as more common in Francophone regions, but participants working in Anglophone regions also found them problematic. Box 5.2 shows participant experiences of this.

Box 5-2 Frequently voiced opinions on public sector stewardship

“And then we have another culture, the culture of not working, getting the benefits but not working, that is a very big problem that we have! You need to show the colour of your money to get papers through or you need to know someone.” **PM5.PPT.1 Trial coordinator in a hospital in a Anglophone region**

“In the English speaking zone, people are more cooperative, but in the French speaking zone it’s a bit difficult because the people are complicated. They always look at, ‘What is my benefit? Where is money?’ If they don’t have any benefit [for them] they can’t help you to realise your work. They don’t care whether the work will benefit the population or not, it’s not their business. They might not even give you the quality of the work, but they want money or they want to gain.” **INT.13.PPT.1 Regional programme coordinator in a hospital in an Anglophone region**

“It’s not difficult [to motivate people] once the person is coming up with an agreed amount to help you. It’s always very, very tricky. People like a lot of money and want to do little work for it, so you need to really negotiate, it’s a challenge.” **INT.2.PPT.1 Director of academic institute in an Anglophone university**

These difficulties often led to poor relationships between researchers and administrators and caused researchers to look for ways to bypass the university systems. A head of a research group based at a university who had set up his own partly separate research unit explained his experiences:

“We try as much as possible to not involve the university because most of the time the university is not organised enough. The administrative bottleneck is a nightmare because you are working with people who you have to be at their mercy... So, they decide when to give you money. He is not working under my calendar, I’m working under his calendar” **INT.3.PPT.1**

Although most researchers were damning of administrative staff, others sympathised that administrators were very disconnected from research, received no benefit from it and therefore had little incentive to improve their performance. Research administrators said that they were under-resourced, under-valued and that there needed to be greater investment in research services. They argued that

they wanted to be more involved in research and could help improve processes but were often prevented from doing so by researchers who only came at the last minute for signatures. Donor financial procedures were also suggested to complicate matters and only ever supported research teams to manage their own budgets. A research services head argued that involving the university systems would be a much more sustainable and cost-effective approach:

“Researchers just come for grant endorsement 24 hours before the deadline. We cannot be seen to hinder research so if it is not obviously a bad proposal we would have to endorse it. But we miss out on an opportunity to develop them and work together which would ultimately lead to better management of the grant if it was successful...We need to develop administration capacity and grant management support to help people with grant applications. But this is never built into grant applications and funders never provide funding for this. They train individual researchers to manage their own grants. But researchers are not skilled in this and have no time – the training and funding needs to go to the administrators. It is better to nominate a project manager from the unit, then train them, and then their skills would be retained and benefit many projects”. INT.7.PPT.1

One institution head in an Anglophone university said that to streamline procedures he was trying to implement clear procedures and performance appraisals. However, a clinician and trial PI in an Anglophone district hospital was very candid that any initiative designed to improve this situation would face heavy resistance:

“Luckily it is changing progressively. But when you start coming with the ideas [streamlining and accountability] she is rightly saying they look at you as a threat. That is because of corruption of the system, if it is well organised like that they will not have the opportunity to collect money from patients, so nobody wants things to be organised.” FGD.1.PPT.1

5.4.4.2 Research regulation and ethical approvals

Regulatory and ethical approvals were a commonly reported barrier to clinical trials because they slowed down research operations and could reportedly cause internationally-trial organisations to be reticent about conducting studies in

Cameroon. However, more recent clinical trials reportedly faced few review difficulties. Although these trials were all studies using previously approved therapeutics or behavioural interventions and were therefore likely to be less ethically and regulatory complex, several participants attributed these better review experiences to recent improvements in regulatory and ethical review procedures and capacity. A regional programme director explained this:

“The regulatory authority takes a lot of time to be able to provide approvals. It means that when external firms like pharmaceutical companies want to conduct clinical trials, with the time that the local authorities take to issue their approvals, sometimes they are discouraged and they don’t come... But, I hear, I have not yet confirmed it, that things are better now.” **INT.13.PPT.1 Regional programme coordinator**

The improvements in ethical review were attributed to increased ethical review capacity at the national ethics committee, and more recently, at several institutional review boards which could relieve the work burden by reviewing local institution lower-risk studies. While some participants still considered ethical review to be too stringent and take too long, ethics board members argued that their requirements were standard and if turnaround times were slow, it was likely due to incomplete applications from investigators who did not plan properly or lacked knowledge of research ethics. However, they did say that ethics boards and regulators still lacked capacity to review more complex trials, particularly novel therapeutic studies, which slowed review because applications needed to be deferred to external experts. Accordingly participants said more training in designing ethically sound research and reviewing applications was needed. As such, this situation was similar to the barriers and enablers to review capacity reported in Ethiopia.

Despite reported improvements, some participants thought that legal regulatory frameworks were still weak and harmonisation was lacking between overlapping regulatory organisations. This meant that monitoring was often not functionally conducted so it was difficult to be assured of ethical and quality standards. A trial PI and IRB member explained her experience of monitoring:

“We have the Ministry of Health, we have ethics committees and institutional, national, all that is going on... But, the monitoring that should go on, they just trust the researcher. There is no real monitoring. I sit on the board of ethics committee of [X] institute and we’ve been talking about monitoring projects but we haven’t done any. It’s challenging, but I must say, we are much better off today researching here in this country than we were in recent years.” FGD.6.PPT.1

5.4.4.3 Research investment and stewardship

Similar to the Ethiopian case study, most Cameroon participants reported that there was chronic underinvestment in research in universities, and healthcare institutions received almost no investment to build research capacity. Some participants attributed this to limited finances caused by a legacy of structural adjustment programmes and many competing priorities. However, most respondents were more sceptical, saying that some money could be found, but research was not a priority because decision makers were disinterested or actively opposed to research. A university research leader explained his opinion:

“You cannot see a building from the state that is a research building. It is not because the state does not have money for that. Those who are making decisions on behalf of the state have a lack of interest for research. It needs pressure from the deans to ensure the government allocates money and the money goes to the right equipment. But the leaders are not leading.” INT.3.PPT.1

This meant that material resources for research were limited and it was very hard to gain local funding for clinical trial projects. One expert stated that the

government allocated less than 0.7% of the health budget to research, which was well below the internationally recommended benchmark¹, and less than 10% of local research was locally funded. This reportedly made the conduct of locally-led trials difficult and unattractive, as explained by this foreign-led trial coordinator:

“We are not really motivated to get into research because we don’t have the infrastructure, we don’t have the resources from government. They expect that local scientists should get money from abroad to answer public health problems relating to our own country. So it becomes difficult as there is not the willingness to support research as a priority. So the investigator will look at the investigator initiated research and think it is really not easy. I’m just coming from Ghana last week. The same problems are there, no motivation from government, infrastructure and the rest...” **FGD.4.PPT.2**

It was a common understanding that the government expected Cameroonian researchers to secure foreign funds for local research, and indeed the vast majority of reported clinical trials were funded by international grants or through research collaborations. The only reported exceptions were 2 locally-led trials that only required small budgets because they investigated the use of behavioural interventions.

Problematically, as was the case in Ethiopia, international grants for clinical trials and other types of research were reportedly very hard to obtain, and only a few local investigators had successfully done this. Furthermore, most had struggled to find further funding. The only exceptions were investigators who had long-term supportive relationships with HIC researchers who helped local investigators to find

¹ The internationally recommended level for health research funding is 2% of national health expenditures 99. World Health Organisation. Ministerial Summit on Health Research (2004: Mexico City, Mexico). Geneva: World Health Organisation, 2005.

and apply for grants and eventually build up research portfolios so they could successfully apply for international grants more independently. Indeed, most participants considered foreign collaboration to be near essential for gaining international funding.

However, several local investigators said the reliance on foreign collaborations could be problematic because local researchers frequently had to change their research ideas to fit donor agendas and some locally important research topics could not be investigated because they were not international priority areas. Funding contingent on working with bilateral partners was reportedly particularly bad because it made local researchers dependent on HIC research groups, which meant they could lose leadership of their studies and if they did not have international contacts then they could not apply for grants. A head of research administration explained this:

“The initiative in the research agenda is taken out of our hands because the funding comes from external sources which means that we have to follow their rules and agendas”
INT.7.PPT.1

A policy maker stressed that foreign research agendas were not imposed on Cameroon because the Ministry of Health worked closely with donors and always had the final decision on what research to permit. However several participants said that there was no clear health research strategy in Cameroon because even though research strategies may exist, they were not implemented. This was attributed by one Ministry of Health worker to disorganisation between the multiple stakeholders:

“There is a Ministry of Research, but you also have university institutions which depend on the Ministry of Higher Education. Another actor of research is the Ministry of Health. They order or agree research that we need to do, but there is a lack of linkage between those

cultures, there is not implementation, because there is no communication.” INT.8.PPT.1
Head of a Ministry Department for infectious disease control

Although this overall situation is similar to Ethiopia, unlike Ethiopian participants, Cameroon respondents strongly felt that it was the government’s responsibility to invest more in research. This is addressed in more detail in section 5.4.8 (page 209)

5.4.4.4 Policy-making and treatment guidelines

Similar to Ethiopian participants, Cameroonian respondents reported that the paucity of local experimental evidence meant that few policies were based on contextually appropriate research. However, Cameroonian participants provided much greater detail on the causes, caveats and consequences of this.

Although many Cameroonian respondents said that more applied local clinical trials were required to overcome the lack of local evidence to inform policy, others argued that even in cases where local evidence was available or could be commissioned, this was rarely done. This was reportedly because decision makers lacked knowledge to interpret and commission evidence. Therefore foreign guidelines were often adopted with little consideration, as explained by this systematic reviewer and local trial PI:

“What happens is they know what the health problems are but they don’t know how to go about getting the best available evidence or trying to fill in the gaps with research. So basically we just wait until WHO recommend something and then we fund that strategy or that intervention, instead of generating local evidence.” INT.1.PPT.1

Other participants said that when clinical guidelines were generated they were often purely procedural because they were rarely disseminated to lower levels

of the hierarchy where implementation took place. A district level public health practitioner who had conducted a locally-led trial explained her frustration:

“What happens, as he was rightly pointing, is that even the conditions that our Ministry say they have guidelines for - You go there [the ministry] you will see ‘Guideline for treating tuberculosis, Guideline for treating HIV positive mother’ - But they keep their guidelines for themselves; they don’t even know what is going on in the nearest hospital. They will go to conferences and they will say ‘Guidelines! Guidelines!’ but nobody will come and say... ‘To be honest I haven’t seen the guidance.’ Not ordinary persons would even have access to them”. FGD.1.PPT.2

The absence of, or failure to use clinical guidelines based on local evidence was of great concern for several participants, not just for patient treatment, but because it reportedly led to a culture where there was little standardisation, recording and rigour which made research difficult. To overcome this it was considered essential to train staff on the importance of following protocols. One clinician explained how the lack of treatment guidelines prevented his involvement in an international study:

“A team from South Africa came to [City X]. They wanted to launch a trial but we had just a few days to work with them and after that we were ashamed that this is a country that when they ask us “Who gives treatment in your country, who has to do injections in your country?” We tell them “no, any experienced nurse, anybody”. So finally the lady who was leading the team was very polite but she told us “I’m sure even a butcher who’s experienced would come and do [surgery X], because you don’t have guidelines.” FGD.1.PPT.1

Despite propositions that local researchers could forge better relationships with policy makers than foreign researchers, many respondents thought that international findings still had preferential status. This was because international bodies endorsed them, provided funding, and pressured decision-makers to translate them. Conversely, local evidence often had no internationally respected backing and was therefore considered less credible by top top-level decision-makers. However, one respondent explained that local evidence was not considered less valuable because of the usefulness of its data, but rather that there

was no funding or support available to translate it into policy, which meant there would be little point in paying attention to it:

“To translate local investigator’s evidence into policymaking, that can take a very long time. I’m saying that because with local initiators, they need a spokesperson, an international person to come and tell them, ‘This thing, we need to take some action. We need to translate this information into policy.’ Because if an international recommendation is made, they also hope that the international organisation can support it financially. So, if it comes from somebody like me, it’s a good initiative but nobody takes it on board. But if I bring a collaborator like [famous scientist] who comes and makes a presentation, and makes the minister appear, and tells them, ‘You know, we can look at some funding possibilities for this.’ Then I can see all of them working hard to sell it to parliament in the hope that some support would come.” **INT.12.PPT.1 Dean of a medical faculty**

It was also evident that policy actors had trouble working together. One Ministry of Health worker (INT.10.PPT.1) said that hierarchical attitudes prevented communication between researchers and policy-makers, and this meant they did not engage or understand each other. Researcher’s responses supported this because they felt they were excluded from the policy process because of top-heavy centralised governance. Commenting on the lack of researcher inclusion in policy-making, an academic director stated:

“It’s because they want to dominate, the usual centralised, dominated, bureaucratic process!” **FGD.2.PPT. 4**

However, policymakers complained that local researchers made little attempt to disseminate findings and this made it hard to know what research had been conducted. Furthermore, failures of local researchers to engage with policymakers meant that policy-makers had no opportunity to tailor the research to their needs. This reportedly led to duplicative research that was often not relevant for policy requirements. To overcome this problem the Ministry of Health recently developed an online evidence repository where investigators could upload their findings to be

reviewed by policymakers. While this was viewed as an important tool, this Ministry of Health worker was disappointed that so few local researchers utilised it:

“We are always bashing heads with PIs but it makes it more difficult to use their results... We are trying to make the results easier to implement. We have just recently launched a virtual labyrinth, where we try as much as possible to upload the results of the research or information that can help any decision maker. So, we are trying to solve the problem...We are trying now to make sure that people use it. But it is disappointing because many people do not use it and they come with poor policy applications [briefs].” INT.10.PPT.1

Many academics acknowledged that research was often for academic progression rather than practical impact, results were rarely disseminated, and they lacked knowledge on how to make research impactful. One experienced trial coordinator explained that the solution was maintaining good relationships with policymakers through regular contact:

“It’s true that it’s a problem trying to get along with the authorities, but once you get to understand them and they know the value of your work then it becomes easier to translate, to advocate for these interventions that are life-saving. It’s easier to integrate with the policymakers if they know you and you come to them pretty often.” PM.5.PPT.1 Trial coordinator

5.4.4.5 Human resource use and development

Unlike participant reports of human resource capacity in Ethiopia, most Cameroonian respondents felt that individuals with the potential to do good research were present, just ineffectually used. This ineffectual use of human resources was attributed to the lack of a “research platform”. “Research platform” inferred a combination of supportive research culture, material resources and financial and career incentives that would foster and reward research. The head of an academic department explained this:

“The research platform doesn’t exist. I have many colleagues, when they are recruited to universities, they don’t have any platform which really stimulates them and lets them know

that research should be a major component of their career. So they are just going back to teaching and they are given administrative duties and at the end their research career is dead. So of course the lack of possibility of research in our university programmes has a negative impact on the research culture...If we could start by using the critical mass we have now, we could manifest research. Even my own resources, which I try to dedicate to research, are not being used properly.” INT.3.PPT.1

Other participants felt that expertise was deliberately ignored or excluded. This was due to reported non-meritocratic selection based on nepotism, or because senior academics did not want to be undermined by colleagues who had a better grasp of modern research. The following experience was accepted to be commonplace:

“People are not conscious of competence - that’s our problem. There are excellent researchers out there who can do research that can help improve different aspects of our country. Why aren’t they using them so that the findings could inform policy? Is it that they don’t know them, or is it that they don’t belong?...The people who ask for this research, they will be looking for either their family, their friends to get what they want to get out of it. Sometimes it is that kind of attitude that blocks research. ” Dean INT.5.PPT.1

Overall, this situation reportedly resulted in skilled researchers quickly getting discouraged and either moving to better paid local sectors such as NGOs, migrating abroad, or gave up trying to do research altogether. This brain drain was seen as a huge waste of valuable resources. One trial coordinator thought that institutions offering fellowships abroad had a moral obligation to acknowledge the lack of research opportunities available when LAMIC researchers returned home:

“The tendency is that they give you the fellowship but after a year it is done, then it’s like ‘You’re on your own.’ The only thing you can say is that you have a qualification. Now the person comes back but he has no means, no ability or opportunity to implement anything he has learned. So consequently it would appear to him as a complete waste of time because the institution that has done his training has pushed him back without any specific support.” PM.5.PPT.1

This lack of accessible human resources for research most strongly impacted on the conduct of locally-led clinical trials within universities and hospitals. However this situation was also problematic for foreign-led trials because it made recruitment of local staff difficult. Although, participants thought that the main solution was harnessing the existing capacity by developing a “research platform” (addressed further in section 5.4.8, page 209), many still considered further training and development to be required. Training needs were the same as those in the Ethiopian case-study, but Cameroon participants also identified skills in management and leadership as important.

5.4.4.6 Material resource and infrastructure availability

Unlike respondents in the Ethiopian case-study, most Cameroonian participants viewed material resources and infrastructure as more limiting to research than human resources. This was because they considered human resources to initiate and work on trials to be limiting, but material resources to often be completely unavailable without foreign assistance. The lack of material resources reportedly not only prevented or reduced the scope of trials, but also reduced motivation to conduct trials when in combination with a lack of funding and access to staff (as was commonly the case). The head of a research department explained this:

“If the person is not sure to have enough funding to do that [a clinical trial], he will not do it. If he is not sure to have the chance to get good team members, he will not do it. Also not being able to equip the laboratory; those are the really important points that can make someone deny to start clinical trials.” **FGD.6.PPT.1 Head of research department**

Reported material resource and infrastructure constraints were the same as those described in the Ethiopian case-study, and like in Ethiopia, this meant that

almost all material resources to conduct a trial had to be provided by the trial grant. The only exception to this was in dedicated research institutes where more established capacity was developed through long-term less project-specific support from international consortia. Material capacity development provided through locally-led or short-term trial collaborations did develop capacity. However, in all circumstances, building sufficient material resources for the site to become more sustainably established was only achieved after conducting multiple research projects. Since this was uncommon, established trial groups were rare. As stated previously, ability to gain multiple grants was almost always associated with having supportive long-term foreign partnerships.

Problematically, lack of material resources sometimes prevented collaboration because laboratory equipment was insufficient for international research needs. Alternatively samples could be sent to the collaborator for analysis, but this meant local capacity was still not developed. The head of an academic department described his experience of this:

“It is difficult, for instance, yesterday a colleague from [UK university] sent a proposal form for the Gates Foundation. So they are looking for bio-markers, but I cannot respond to such a call because the platform of technology behind the identification of bio-markers, I don’t have it. I have 3500 samples which we have collected from patients with various conditions and sensitivities. But we need to be associated with partners that have the technology to identify those biomarkers. So the best we can do is to send our samples and research assistants abroad to participate in those studies.” **INT.3.PPT.1 Head of academic department**

Positively, the national government was significantly developing the material capacity and infrastructure of several new and established universities’ medical departments. However, several participants suggested that financial and operational mismanagement wasted investments when they were made. An

academic director explained his frustration with recent building works at his university:

“So we are building there a brand new building, but there is no electricity, we will use a generator. I mean how is that possible? It’s supposed to have the electricity before the building was finished, it should have been ready and even the water is not working. So these are the type of misplaced priorities I’m talking about.” **INT.2.PPT.1**

5.4.4.7 Awareness of trials, motivation and self-efficacy

Lack of awareness of trials and low motivation and self-efficacy to conduct them were as problematic to local-led trial undertaking in Cameroon as they were in the Ethiopian case-study. The reasons given for the lack of awareness in Cameroon were the same as those described by Ethiopian participants. Once again, healthcare workers were considered to have the least exposure to trials. Box 5.3 shows participant opinions selected from the many expressed:

Box 5-3 Opinions on the impact of limited exposure to research

“I think people first need to be taught how to conduct a project of research. Many people don’t know what it is. We teach them different skills, but it’s not on research. Many people don’t know what to do when you say, clinical trial. They don’t really know what a clinical trial is. They do it because one has seen the others and he imitates. But because no-one does them, no-one does clinical trials” **INT.9.PPT.1 Vice Dean**

“Most of us do not have the right exposure to clinical research. I can be talking close to the scientist, but with the clinicians it is different. All of them have heard about research, but a randomised control trial, most of them found it difficult to understand.” **PM.5.PPT.2 Chief Medical Officer**

“If I talk of ophthalmology, the training, at different schools of training we don’t expose people to research.” **FGD.4.PPT.1 Lecturer**

The reasons given by Cameroonian participants for low motivation to conduct and work on trials were also similar to those described by Ethiopian participants. As this young locally-led trial PI explained, initiating a trial requires extended periods of hard work and effort that some researchers may not be motivated to undertake:

“If you decide that your question is best answered by a clinical trial you need to be able to determine your sample size, you need to be able to perform a good randomisation, you need to be able to prevent losses to follow up. You need administrative clearance from the Ministry of Health, you need ethical clearance from the National Ethics Committee. You need to go through all of these hassles. And finally you need to be able to analyse your data at the end. I mean when people look at the long list of things ahead of them, you know, and how much time it will take before they get one paper published, it can be very discouraging. They just shy away from trials. INT.1.PPT.1

Therefore participants said that most individuals expected to be remunerated for the extra work that clinical trials entailed, especially when time spent on research reduced salaries from second jobs. Payment was a particularly important for healthcare staff because they were very busy and were unlikely to receive career progression incentives. This was problematic because most clinical and even academic staff reportedly had no extra salaried time for research and payment from individual studies was sometimes negligible, not even covering personal expenses. This resulted in a lack of motivation to conduct research, as explained by this PI:

“Now the first difficulty was to try to create a team because people have many other problems and they are not motivated [to work on trials] because they feel that they don’t have enough time to look for means to first feed themselves, so they fail to have time to reserve for research which will not bring them anything. That is those among the care providers; they don’t feel benefit in terms of money, in terms of what it will bring into their career, they don’t see any immediate benefit!” FGD.1.PPT.1

Apparently this problem was recognised by the government as they had recently started offering research allowances for clinicians. However this was only reported

by a few participants and the coverage and success of the programme was not clear.

Career recognition for research was reported to be a very important motivator. However, this was only the case when career progression was linked to salary increases and working condition improvement. In many universities there was an emphasis on providing support for teaching, with research seen as additional “side” work outside normal duties. This meant that although research was required for academic progression, it had little impact on working conditions and it was possible to earn similar salaries by only teaching or performing administrative work. For non-academic healthcare staff, research was even less important for career progression and salary increases. Accordingly many people saw little point in conducting research or rapidly lost interest in it, as an academic explains:

“The state take people who don’t understand research culture – they take people who teach. If you are a teacher you come here, they will give you a job, they will give you a platform! But you never see post-grads in laboratories. Most of them are teachers. The teachers to some extent look at the situation and say ‘okay, why should I have a research position? As a teacher I have allowance, I can get extra hours, I can get some money from the budget.’ So why should they bother pursuing research?” **INT.3.PPT.1**

Despite the importance of working condition improvement and salary incentives in determining motivation to conducting research, there were some intrinsic incentives identified by Cameroonian participants that if present, encouraged them to conduct research despite other poor incentives. These were similar to the intrinsic incentives reported by Ethiopian participants and included: learning new skills, satisfaction from successfully running a trial, receiving praise from colleagues, and helping improve community health. Leadership and responsibility for research was reported to be particularly motivational because

responsibility not only ensured ownership over trial outputs, but also gave status, recognition and allowed individuals to take on new challenges and show initiative.

The PI of a locally-led trial explained his experience of this:

“I felt like I was recognised as a scientist when they allocated the funds for me to manage. I felt like, ‘okay, they recognised that I could be a leader and they have given more responsibilities’, and that gave me more courage. It also motivated me in the sense that I would always be the principal investigator, so if, for example, there is a presentation somewhere I will probably be able to go for this presentation and also stand up among other peers or scientists, among everywhere, and talk.” **FGD.1.PPT.1**

Although some junior trial staff said they would prefer to work on foreign-led trials because of their better resources and externally managed operations, senior researcher respondents disagreed, saying that they would be more motivated to work on a locally-led trial. This was because locally-led trials would provide more opportunities for responsibility, ownership and recognition:

“If I were to be involved in a project which has been piloted from outside, I would do it in a very relaxing way. I will do the defined task of collecting samples etc., but you think that you are just executing a sequence of a process. You do it because they give you money – probably you benefit from some overheads and participate in publications, but rarely are you the first author. But if you were to carry out a clinical trial which you designed, you can take full responsibility for what will come as good or as bad. All international recognition will be yours.” **INT.3.PPT.1 head of academic department**

As reported in Ethiopia, lack of self-efficacy to undertake locally-led trials in Cameroon was reportedly caused by perceptions that clinical trials had to be complex and resource-intensive. Like Ethiopian participants, Cameroonian respondents suggested that greater exposure to clinical trials, particularly seeing examples of them being successfully conducted, would increase researchers' self-efficacy.

However, Cameroonian participants also explained that it was important that individuals were exposed to locally-led or simpler trial designs, as only seeing international drug trials conducted reinforced the perception that trials had to be complicated². This situation reportedly led to few local researchers initiating “simpler” behavioural trials, despite expert opinion that they would be highly useful, appropriate and easier to conduct. Indeed, one clinician explained that he became more motivated to work on clinical trials when he realised that they did not have to be complex drug interventions and were therefore achievable:

“It motivates me to realise that a trial doesn’t necessarily have to be a drug intervention trial, you know a simple intervention like sending out text messages for example, might be a good enough. I think it has really interested me. So it has been important to realise the different potential of practical simple trials that can be implemented in my community in every aspect. So I think when next there is a clinical trial hopefully I will make a contribution.” **PM.4.PPT.1 Clinician**

Another important promoter of self-efficacy identified by Cameroonian participants was trial knowledge and experience. Respondents who felt they had skills gaps were very reticent about leading their own studies, but when researchers with low levels of self-efficacy gained knowledge and instructive trial experience, it greatly increased their confidence, as one nurse explained:

“I first of all thought that I could not do it [coordinate a trial] because I’m a nurse. I was asking him [PI], ‘Do you think I will understand this?’ But, I came to understand that actually my opinion counts, that I had something to say. We came up with this proposal and it was approved, and I saw my name as a coordinator, I go ‘wow!’ Like even as a nurse, I can recognise that I can do something. So, that was a very big push for me... Yes, I feel more confident talking because I’ve read some literature reviews, I’ve realised the results and I see that I feel really confident when we I’m talking about injections now based on the policy I’ve already read.” **FGD.3.PPT.1**

² After participants described their perspectives on types of clinical trials, it was clarified that this study was interested in a broad perspective of randomised control trials encompassing novel and approved interventions and behavioural trials.

However, the most important promoter of self-efficacy appeared to be trial leadership experiences because this gave opportunities for responsibility and ownership that forced individuals to develop their own ideas and proved that they could successfully lead a project on their own. Conversely when opportunities for involvement and contributing to the trial were limited, as was common on some foreign-led trials, especially more short-term collaborations (see section 5.4.6, page 202), self-efficacy and leadership were not developed. This was reported by several participants in Cameroon and may also explain the observation in the Ethiopian case-study that participants who had considerable experience of working on foreign-led trials still did not have self-efficacy to lead their own. One participant's (FGD.3.PPT.1) experiences clearly illustrate this. He worked as a clinician in a district hospital and had taken part in several foreign-led research collaborations, then after some years he was able to gain a small grant from the WHO to lead his own trial because they had approached him about how to improve a specific healthcare practice which was problematic in Cameroon. Describing these mixed trial experiences he said:

On the other [foreign-led short-term] collaborations that I'd had in the past, they just told me, gave me clear things. 'Run this questionnaire,' and I just ran the questionnaire. I don't even know the principle behind the questionnaire, why this is asked like this, why that is asked like this. I said that "maybe there is a need for me to train some people?", but they say, 'No, that is not part of the work we want you to do". They just wanted us to collect the data. So you see we didn't learn and develop...

...But on our X trial [locally-led] we got to really face a lot of challenges and overcame them and then through that we developed. Through that we got more mature. I think one proof that the X trial was very instrumental in building our capacity was that we've been able to develop some more ideas in a more refined manner. We have a saying that 'the son shows maturity when he picks up his arrow and goes hunting'. It's an African saying. You know that the son is mature when he picks up his arrow. He doesn't wait for his father. He

doesn't wait for his uncle. He just goes hunting. This is what I think I have been able to do more with the other [locally-led] trials. FGD.3.PPT.1

However, this participant (FGD.3.PPT.1) had not conducted any further trials despite frequent efforts, because he was unable to secure additional international funding and he had trouble finding collaborators to support his trial plans. Therefore although he had the skills and mentality to lead trials, resource shortages prevented him from continuing to do so.

Opportunities to take on responsibility and make a contribution were also prevented by local institutional structures that were resistant to delegation of responsibility and bottom-up changes. Some participants argued that this led to feelings of apathy and giving up trying to make a difference. This was especially true for individuals trying to make changes through research because such initiatives were not appreciated and had no impact. A Ministry of Health department head described his experiences of seeing colleagues giving up trying to conduct operational research to improve policy:

Over the years, people have the tendency-, they don't care anymore. Some of them have tried [to make a difference through research] and they've failed, they never get recognition, so they got tired of trying. So they either move away, or you will be a passive worker. INT.8.PPT.1

5.4.4.8 Local collaborations, teamwork and mentorship

The importance of local collaboration and the difficulties encountered when attempting to form collaborative teams in Cameroon were very similar to those described by Ethiopian participants. However, Cameroonian participants provided greater detail on why local collaboration was so rare and the wider consequences of poor team working.

Several respondents suggested the lack of local collaboration was due to local researchers often not being known to each other. Therefore some suggested that a registry of local investigators should be compiled to identify investigators and facilitate networking. This was also seen as a useful tool for showcasing local expertise to potential international collaborators, as the head of a provincial health faculty explains:

“Networking that’s a big gap. You see we need awareness of each other first. In Cameroon, there’s smart people but the knowledge just stays there, nobody uses it. In Africa, people don’t know each other exist and so cannot maximise resources and cannot work together. We need to map out expertise on a system or database. It will also give an opportunity for North-South collaboration. .” **INT.12.PPT.12**

However, participants from all professional fields reported that local collaboration was not just uncommon due to lack of local contacts, but also because team working was a difficult and unpopular prospect. One of the reasons given for this was that researchers were encouraged to be competitive and individualistic by the way grants were administered and how academic success was measured, as explained by this academic director:

“So people are encouraged to apply for small research grants for themselves, so that they can publish papers for promotion purposes. So that culture now is embedded in people, so people don’t see the relevance of putting up a good proposal based on contemporary teams and then compete for donors funds. They don’t see that you are bound to do better research that way.” **INT.2.PPT.1**

However, most respondents felt that it was the general Cameroonian work culture that made collaboration and teamwork inherently difficult. This was reportedly related to hierarchical cultures that made it difficult for Cameroonians to work together on an equal footing. Arguments over who would lead projects and receive recognition prevented cooperation, and very often there may be several

individuals trying to lead a project. Participant experiences of local collaboration are shown in box 5.4.

Box 5-4 Participant experience of being dependent on foreign funds

“There is a lack of culture, there is fighting. There is a lack of recognition. If a product is coming and there will be money everybody is going to be interested in it. Who is going to work? Who is going to contribute? Who is going to be the PI? You see, the PI might not be the person who is going to do the real work because of ‘What is your name? What is your title?’” **INT.8.PPT.1 Ministry of Health department head**

“There is a lack of organization, we have to organise as a team, we have to network. Having research in multidisciplinary teams is something that I keep saying is needed. People have to learn to work together. In this country they don’t. In most of Africa, maybe... Whether it’s something I did wrong I don’t know, but it’s just very difficult to get people to work together. Everybody wants to be the boss of his own thing, so that doesn’t make it easy.” **INT.14.PPT.1 Academic director**

“This is difficult because when in Europe, you have the spirit in your team. Whereas here we don’t have it. We have different interests and we are not at that level where we have, let’s say, the maturity in research whereby we can understand that we can do one thing at a time. It’s usually several points to several objectives.” **FGD.4.PPT.3 Clinical head**

This lack of collaboration and organisation meant that it was reportedly hard to harness the extant human resource capacity and pool material resources to reach the critical mass required to self-sufficiently conduct more ambitious work and successfully compete for international grants.

Another frequently reported and related problem in work relations was professional jealousy, insecurity and lack of trust among local individuals who attempted to conduct research within this competitive and challenging environment. This not only prevented people from working together but also supporting each other, particularly junior researchers. The reason given for this situation was that top level academics felt entitled to project leadership and any benefits arising from

junior colleagues' research, regardless of their involvement. If colleagues were more successful than them, or they suspected that they would not receive direct benefit from others' research, they were reported to try to sabotage research efforts or try to steal the credit. This led people to become wary of sharing ideas. One participant said that these attitudes were particularly problematic regarding clinical trials because senior academics did not understand them, so they did not want younger researchers who understood the method better making them look stupid. Once again, participants said that these attitudes were more common in francophone Cameroon, but they were also reported in Anglophone regions. Illustrative experiences of this are shown in box 5.5.

Box 5-5 Experiences of professional jealousy and mistrust

“Researchers still remain a big problem to other researchers, because that jealousy, the envy is still there. For young researchers, the elder ones do not hold our hands to take us up. If it does not suit how the elder person wants it to be, it means it is not good and he blasts everything...They also look at the benefits that this young man may have from this. If they are not going to make a lot out of it too, then they may not give you, we say in French ‘soutien’, their benediction to push you ahead. We still have that in our milieu, especially in the Francophone zone...If you produced a good piece of work, they used to want to knock you down, ‘Who are you to be famous?’ People instantly try to sabotage it. But that mentality is gradually fading out.” **INT.13.PPT.1 International research fellow**

“It’s a bit difficult discussing something with them [senior academics] and working as a team. It is difficult because most of the time we will think that if we share our idea, maybe even if you initiated the idea, at the end of it you may not even be included and someone else earns the credit.” **FGD.1.PPT.1 Local PI of international trial**

“And then people get reticent about sharing knowledge, they think “Oh he’s going to make me look stupid, he knows more than me so...” So those are some of the cultural blockages that we have here, people are afraid of sharing, people think that they may expose their inefficiencies or deficiencies, it’s a terrible thing.” **INT.2.PPT.1 – Director of academic department**

“Clinical trials are a new concept which we are still trying to adapt to; it is this younger and new generation of researchers who are trying to use it. And so invariably at times there seems to be an obstacle with the higher generation, the younger generation depend on the bigger ones, the professors for support, but since clinical trials were not in their culture per se, they seem to obstruct the initiative from the younger generation.” **PM.4.PPT.1 Young trial investigator**

5.4.5 Trial operations and management

The system-wide barriers to trial conduct mentioned above introduced various hurdles to trial operations. These operational hurdles were very similar to those experienced by participants in Ethiopia. The main operational issues experienced in Cameroon by participants working on all types of trials, in all institutions, are shown in table 5.2.

Table 5-2 Operational issues reported by participants in Cameroon

Operational stage in trial	Operational experiences reported by participants	Drivers of operational experiences reported by participants
1. Thinking of research ideas	• No difficulty	• Initial research experiences often sparked interest in conducting research • Ideas usually came from noticing problems in daily practice
2. Securing funding & sponsorship	• Local funding was very scarce • Many participants had difficulty writing grant applications and competing for international funding • Rigid funding made optimisation of trial operations difficult • Financial constraints either prevented research or severely limited the scope of the study	• Limited research investment • International funding highly competitive • Not enough early planning for grants and too little inclusion of university administrators • Foreign-led studies normally had little financial flexibility • International collaboration and support helped with grant applications
3. Developing the protocol	• Few issues reported, although many respondents daunted by randomisation and power calculations	• Little experience in statistics
4. Securing ethics & regulatory approvals & admin permissions	• Few problems with ethics approvals but many participants found research guidelines overly complicated and confusing • Regulatory approvals for approved drugs & low risk interventions usually not problematic • However some reports of regulatory approvals & getting licences to import off-list drugs taking over a year • Admin permissions could be problematic depending on the number required & the decision makers research inclination	• Some misunderstanding why there should be different principles and guidelines for clinical care and clinical research • Ethical and regulatory capacity was reportedly functional due to capacity development successes • Bureaucracy meant many levels of approvals were required & some decision makers were disinterested or suspicious of research & held up permissions
5. Completing administration tasks	• Accessing locally held funds was difficult & disbursement was slow • Purchasing was very slow, sometimes taking up to a year before products were received	• Bureaucratic procedures meant multiple forms and permissions were required • Near absence of administrative research support • Investigators often bypassed system to avoid delays

6. Completing logistical tasks	• Logistical tasks for clinic based work was not reported as problematic, but field based research was difficult if resources were scarce, particularly transport, accommodation and communication	• Limited funds to meet logistical needs • Poor transport & communication links in rural areas
7. Recruiting, managing & training staff	• Research skills were not common, so forming a skilled team can be difficult, especially because of limited teamwork culture • Participants said it was essential to train staff in good research practice e.g. GCP • Poor pay and minimal research incentives make it hard to recruit and motivate staff to take on additional work • High staff turnover	• Research cultures in many institutions are weak • Individualism and lack of trust prevent teamwork • Few good research leaders and trial managers • Limited previous exposure to research • Little budget for research and foreign studies reluctant to pay local salary incentives • Staff look for jobs with better condition • Health service partners regularly rotate staff
8. Setting up & running a laboratory	• Laboratory infrastructure and resources were commonly lacking, especially in more advanced equipment, which limited research scope • This meant samples may have to be sent abroad for analysis or researchers could not take part in international collaborative projects because essential capacities missing	• Laboratory capacity was mostly limited by financial constraints • Difficulty purchasing and procuring lab supplies made lab management difficult
9. Recruiting & managing patients	• Patients, particularly in rural areas, can be sceptical and fearful of research • Research incentives are normally required to facilitate recruitment	• Previous unethical conduct, cultural beliefs and lack of understanding of research make people reluctant to participate in research
10. Data management & monitoring	• Limited trial resources and clinical care capacity made complying with regulatory standards difficult • Data management & statistics skills very limited • Poor telecommunications made adverse event reporting difficult	• International research standards not suitable for low resource settings • University infrastructure and services often lacking due to underinvestment • Insufficient statistics training available

As suggested in Ethiopia, several Cameroonian respondents emphasised that the key to avoiding or coping with many of these hurdles was advanced careful planning and effectively coordinating teams. However the critical element for successful trial operations appeared to be good leadership. Indeed, many participants said that good leaders were integral to research success and were critical for increasing clinical trial output in Cameroon. Among the characteristics that ideal research leaders should have, nearly all respondents thought that good team management and mentorship were most important.

Despite complaints that there were few good research leaders in Cameroon, several participants gave examples of local inspirational leaders and mentors who had ensured the successful running of trials and developed staff capacities through good management. All of these examples suggested that good managers inspired staff and promoted teamwork by encouraging professional development and making everyone feel valued. This was demonstrated through: inclusion in training, sharing of research benefits, giving recognition for good work, listening to everyone's opinion and encouraging sharing of ideas, trusting staff and allowing opportunities to take responsibility, and supporting personal development and career progression. In terms of mentorship, the key aspect was being supportive but at the same time allowing freedom and challenging mentees. One project manager gave a detailed account of her experiences of good research leadership; the quotations below are extracts of a longer discussion:

“One [of the problems] is sustainability of the team. But he [PI] has a career development mentality, so by the time you are coming out [finishing the trial] you are totally different from the way you were before. So it’s one of those things that sustained the group. It is an encouragement for people to stay...”

...He helps us to know that if anything good is coming out, it is good for all the team. Everybody is given equal opportunities to get additional training. He makes people comfortable and feel like their opinion counts, though they are students, though they are junior researchers, their opinion, their role in that group is important. As part of the team I think you feel very proud, it encourages you. In this way, this kind of a team spirit is encouraged...

...When someone is only given instructions I bet you will not learn anything. In our group you are taught everything but you are given a chance to express yourself. It's not like the professor does everything, everyone is involved, if you are leading an aspect you do it right up to the end, the professor is there, he guides you, but you have to show him what you have at the end. If he's not available to go for a meeting another team member will go, so that encourages you like 'oh he must trust me up to a level where he lets me represent him and present our study'." **INT.15.PPT.1 Project manager**

These accounts on the importance of good leadership and management are supported by the findings from the Ethiopian case-study where poor team management reportedly led to ineffectual use of staff, essential skills gaps, and dissatisfaction with work. Several Cameroonian participants said that it was very important to develop more good research leaders. Suggested methods for this included: international fellowships, offering more trial experience and responsibility to potential leaders, and one local institution reportedly offered a good course in research leadership.

5.4.6 International collaborations

Like in the Ethiopian case-study, collaboration with the international scientific community was considered by most Cameroonian participants to be essential for clinical trial conduct, even locally-led trials. This was mainly because North-South partnership provided support that was not available locally. Often this support went beyond funding and material resources with many local researchers and students benefiting from training visits abroad, foreign experts giving training and advice locally, and access to literature and knowledge.

However, international collaborations were also valued because of the perceived importance of global scientific exchange. Not only did this reportedly make research appear more robust but also exposed Cameroonian researchers to new methods and ways of thinking. Indeed, respondents said they liked working with foreign colleagues because they found them more open, sharing, intellectually stimulating, better at team working, and less critical than Cameroonian colleagues. They also appreciated receiving support and encouragement, particularly with scarce skills such as statistics and writing grant applications and publications. Being part of internationally recognised research groups also reportedly brought credibility to Cameroonian researchers, which helped strengthen their grant applications. Indeed, like in Ethiopia, nearly every investigator who had conducted a locally-led trial said that foreign collaborations had helped them do this. When collaborations were based on close personal connections and long-term regular contact, they were reportedly even more valuable, as explained by this PI:

“So, whatever is missing, I can go and I say ‘[nameX], there was this paper that came out and I didn’t get it. Can you please? I think that has been so important. I can get information on what is happening outside. We discuss the project and try to keep with the science. I have sent all my technicians there [U.S. University]. Some have been twice for training and have come back. Many students from there have been out here. I think both ways, it has been very, very profitable for both. It’s a win-win. It’s been that way with [nameX] and us. We get the results.” **INT.14.PPT.1 Academic Director**

A consistently valued and highly applauded benefit of international collaborations was when effort was made by the foreign partner to create a local “research platform” through investing in local laboratories and infrastructure and strongly including and developing local staff. This meant that samples would not have to be sent overseas for analysis, the scope of local studies increased, and

there could be better training provision for local researchers. Overall this reduced academic isolation by moderating research inequities and provided greater professional visibility through fostering stronger research profiles. This in turn could have a positive knock-on effect for the wider institution, as explained by this participant:

“Participating [in X consortium] has given us this opportunity to build collaborations with very good researchers. People now know that we exist, and that is good. We have the capacity now to go and develop. All my students are going to learn clinical training. I don’t have any problem with that now I have an infrastructure. Because I have relationships [collaborators] and infrastructure that can help, even the institution is doing good research. The platform where they can do good research has automatically enhanced the quality of training. Because when you go to this university, our laboratories come first now in terms of quality of infrastructure, quality of training of our students. They are really appreciated.”

FGD.6.PPT.1 Head of research department

A widely cited good practice example of research partnership and local capacity development was that of the Central African Network on Tuberculosis, HIV/AIDS and Malaria, part of the Network of Excellence for clinical trials set up by The European and Developing Country Clinical Trial Partnership. Participants greatly valued that one of the project goals was to build a sustainable research platform so that academics would have good facilities, working conditions, and rewarding career paths after they completed their research training; the hope being that this would reduce brain drain. However, capacity development through long-term trial partnerships was not only restricted to consortia investment in dedicated research institutes. A few smaller scale partnerships with Northern academic groups had also established apparently sustainable local capacities within university departments. Such praise was not just limited to long-term partnerships though. Short-term commercial and non-commercial trials also reportedly helped develop local

facilities, provided valuable technical training and jobs opportunities, and improved community healthcare and living conditions.

However, many respondents said that it was difficult to find foreign collaborators, because they lacked the international contacts and collaborators were sometimes put off by the lack of local research capacity. Furthermore, despite these many advantages of international collaboration, not all experiences were positive or resulted from choice. Rather the lack of local funding and resources meant that if researchers wanted to conduct more ambitious research like clinical trials, there was no option but to work with a foreign partner. This dependency was considered to make local researchers vulnerable because they were so desperate for collaborations they may accept exploitative terms. A few participants were also concerned that local institutions missed out on overheads, retention of trial resources, and administrative capacity was not developed because collaborative grants were usually managed by the foreign partner, or routed through parallel systems set up locally.

Most reported problems with international collaboration were associated with short-term trial collaborations because on these studies the foreign partner had almost always designed the protocol, often before approaching local collaborators, and maintained strong leadership over the project. As such local inclusion in leadership and contribution to decision-making was prevented and local roles were restricted to recruitment of patients, data collection, or procedural tasks. Only the bare minimum of training was sometimes provided so local staff may not understand the rationale behind trial activities. Foreign attitudes that local capacity was limited and only useful for simple tasks were reportedly commonplace, with one ministry

regulator describing local investigators as being “just like a carrier” (INT.10.PPT.1) and another saying that foreign groups “assume we have no competence” (FGD.3.PPT.1). If local researchers made attempts to offer opinions and make improvements, these were reportedly ignored by the foreign partner, and when research samples were sent abroad for analysis local researcher’s skills were not developed and they sometimes received little recognition for their work. Overall this collaborative model reportedly failed to develop local capacity in any meaningful way and contributed little towards local researchers’ professional development. Some of participants’ experiences of being dependent on foreign collaborators are shown in Box 5.6.

Box 5-6 Experiences of being dependent on foreign collaborators

“Now we may have the people, they are around here, but we can’t do clinical trials on our own. To be operational, to conduct research at a higher level, you need foreign collaboration in one way or another.” INT.3.PPT.1 Department head

“The challenges that I had were quite many, but I think in particular the fact that I did not have a free hand to decide what could help the trial move forward in my local setting was a big problem. You see every instruction came from London. For example, at a certain point I thought there was a lot of knowledge gap in the doctors, and if we had given them a good training on this there is the possibility that they could recruit more patients and do things better. But this was not possible because London was not focused, was not interested in doing this capacity building. They felt that we should just keep recruiting. FGD.3.PPT.1 Local PI on an international study

“Material transfer, that is a problem that we have, because there are times when we just collect samples and they are sent away. They are taken away from the local initiator, and the foreign investigator is taking all the results and using and analysing and publishing all the data without the other [local investigator]” FGD.2.PPT.2 Associate professor

This led several respondents to say that locally-led studies would result in better capacity development as local institutions would retain overheads and there

would be more opportunities for involvement and responsibility which would improve learning and professional development. This was because locally-led trials would allow researchers to learn by making mistakes and coping with challenging situations, through a process of “learning by doing” (FGD.3.PPT.1) or “training by doing” (INT.11.PPT.1).

The few participants that discussed South-South collaborations were not enthusiastic. This was because they could see little purpose in partnering with another poor institution. An academic head frankly explained this:

“Within Cameroon, it is difficult. You collaborate more with people outside than inside. But even the south to south communication is very limited, especially compared to north to south. I think the problem with south to south networking is that it is very difficult if two people are poor, they come together and they remain poor. It is not attractive for someone who is poor to attach to another person who is poor.” **INT.3.PPT.1 Head of academic department**

5.4.7 Individual enabling characteristics

In addition to leadership skills, a number of other individual enabling characteristics and interpersonal skills were reported by participants to help in conducting research, particularly clinical trials. Given the challenging research environment, both in terms of resources and operational complications, participants’ said that it was important to be persistent but patient because processes could take a long time and may need regular pressure for them to progress. Others said that because clinical trials were new to most institutions, being proactive and reacting positively to problems by being flexible and innovative was essential for finding solutions to apparent barriers. For instance, one investigator had to form an institutional review board to review his trial, as none existed but local review was mandated. Box 5.7 shows selected reports of these behaviours:

Box 5-7 Reports on of the importance of persistence, proactivity, patience and reacting positively to problems

“In our society you need to always put on pressure and nag and fight to get what you want. If you don’t, nothing will happen.” **INT.3.PPT.1 Department head**

“I sit during my free hours and try to figure something and I start writing. I just keep it [research and clinical trial proposals] in case things change and they start thinking that research is important and maybe want to put some means in. I also plan to propose it [research proposals] to foreign collaborators. If they are interested they can also help with the funding.” **FGD.3.PPT.1 Investigator on foreign and local trials**

“You have to be patient. You have to be very patient. So, you should be somebody who is not easily discouraged by challenges that you face. I have gone through a lot of things, ups and downs and now that I’m getting settled and doing all of this and having all this experience, I don’t think it’s time to stop. It’s time to start!” **PM.5.PPT.1 Trial coordinator**

Another reportedly essential skill was the ability to negotiate decision-maker buy-in. This helped researchers to gain permissions and advocate for greater allocation of resources which was critical in environments that were unreceptive to research. To overcome negative attitudes, participants said the key was making people understand what the research involved and the importance for patients.

“At the preliminary stages of the trial you have to advocate, you have to focus to bring different stake holders on board, at various levels, from the central level to the periphery levels. You clearly need to have this ability of convincing people of the truth, to see the necessity [of the study], so he [decision-maker] will give his consent. Because if there is necessity for that intervention, then you can bet your life he will facilitate it. So showing the need, that’s the highest importance.” **INT.3.PPT.1 Head of academic department**

These networking skills were also reportedly very important for forging international collaborations, which as stated previously, were near essential for trial conduct. Indeed, a Dean said that to be successful in research in Cameroon, persistent “marketing” and “solicitation” to international collaborators and funders was essential:

So I feel that it is a mentality - you must have the industry and will to work. I don't sleep, I am on the internet three or four times a day because I don't want to miss anything. So it's a form of marketing [forging collaborations]. I am always pushing. Some people have it, others don't, it's not their fault, some people can't go on pushing. I don't care if you laugh when I've finished, but you have got my message and you will listen one day. So it is a question of mentality and it's a question of patience and endurance, because you are soliciting, you don't have anything, so you must solicit [for funds through collaboration].
INT5.PPT.1

5.4.8 Developing a research platform

Participants made it clear that without developing a solid research platform, the number of locally-led clinical trials was unlikely to increase. They emphasised that this platform should concentrate on harnessing the existing capacity in Cameroon, particularly the human resources which people felt were being wasted. Critical components included a complementary combination of adequate funding, research infrastructure with hi-tech equipment, and skills training to make the most of these resources. Some also said that more exposure was needed to encourage research involvement and trial undertaking, and better incentives to retain staff and attract expatriate researchers home. The Dean of a medical faculty explained his vision:

"We have said that the culture of research, we need to get it to a prominent place – for that we need communication to make people understand the relevance of research. That will come down to the development of a platform for research in universities. So that platform of research will require infrastructure, it will require equipment, it will require skills – technology transfer to function! So I think if we have both the awareness and the means, because when we have got a platform in place we need the means [funding] to do the work." **INT.3.PPT.1 Head of academic department**

Training was also an integral component of the suggested research platform. This was not just to resolve specific skills gaps. Rather participants argued that research training encouraged appreciation for clinical trials and increased motivation to conduct them because people valued updating professional training

records and showing their competence. Others said that training in professional standards fostered a culture of excellence, pride in work, and improvements in practice, as this local PI of international study explained:

“Before I didn’t really understand clearly what doing a clinical trial entails. But the opportunities that I’ve had so far being trained in good clinical practice has brought a lot of pride. It’s bringing a lot of professionalism into what we are doing in terms of quality of care that is offered to patients, in terms of recording what is being done, and in terms of even initiating research in the future. So those are some of the opportunities [of training].”

FGD.1.PPT.1

As also suggested in the Ethiopian case study, to achieve sustainable training capacity some Cameroonian participants had been on training-the-trainer courses and found the training model very useful. Others suggested that research training should become more integral to curricula, with refresher courses and on-the-job training based on local context specific examples. This was especially important for health personnel because they could provide valuable research outputs but were currently outside the conventional research system, as this participant explains:

“The clinicians, the health personnel, are clinically oriented, they are not research oriented. We don’t have too many pure researchers per se, and I think if there can be improvement in teaching of research methodology in the curriculum of medical schools, in the curriculum of the nursing institutions, the institutions of midwives, that would help. If there can be continuous medical education sessions, or refresher courses on research methodology and the importance of carrying out research, it would go a long way to improve upon the knowledge and the technical knowhow of the personnel, and facilitate the necessary research enormously.” **PM.4.PPT.1 Clinician and trial co-investigator**

Other popularly suggested training modalities were mentorship, foreign research fellowships and online training. Local mentorship was particularly valued because it could provide local knowledge on expected problems and the best way to go about resolving them. International training fellowships were felt by one clinical academic

to be the backbone of creating future research leaders, but to be useful a research platform had to be ready for fellows when they returned home. Online training was popular because it could fit into busy schedules, was cheap or free, and required no travel.

However, as also suggested in Ethiopia, actually getting research going in institutions and participating in trials was seen as the best way to develop human resources and a research platform more generally. This was because conducting trials could have a positive knock-on effect of stimulating research and clinical trials institution-wide. These effects are shown in box 5.8. Among the many effects of working on trials, fostering of team working behaviours was regularly cited as an important outcome. These positive outcomes were then suggested to result in a positive-feedback loop that would permit more clinical trials. This led several participants to suggest that pilot or seed grants to conduct small-scale locally-led trials would be very useful. Box 5.9 shows participant experiences of capacity development from participating in trials.

Box 5-8 Proposed capacity development benefits of trial conduct

- Exposure to research for whole institutions increases interest in trials
- Learning new techniques, skills and standards through “learning by doing”
- Access to expert advice and guidance
- Encourage critical thinking, improve management, and create research leaders
- Foster a culture of excellence and raise professional standards
- Reinforce teamwork and collaboration
- Build self-efficacy through training and realisation that trials are achievable
- Increase motivation to conduct research through creation of research careers
- Accumulate resources through progressive successful grants and collaborations
- Encourage investment by showing the importance of research and evidence-based practice.

Box 5-9 Experiences of capacity development from participating in trials

“Clinical trials reinforce team work and collaboration because people tend to work in isolation and that’s not good and we learn more by this type of collaboration and cross fertilising ideas and from related skills.” INT.2.PPT.1 Academic director

“Getting exposed to different aspects of research and working with different groups of people is an experience you really can only have if you are part of it [clinical trial]. Your knowledge increases, your understanding, you have to think deeper. Interacting with high profile professors who are very experienced, I learned a lot. I was improving so by the time I did it the second and third trial, because you’ve been involved in all of this, you can stand and talk very broadly.” INT.15.PPT.1 Trial Project coordinator

“Their [local investigators] initial kick start came participating in a big international trial and then when that trial is over you want to continue with that kind of research. It is my conviction that if we have the means, we will take the opportunity and do a trial. It may not be perfect, but it will build capacities. Once they are capacitated, we can proceed. We can do many other things together. So we need just one chance. Just one, the rest will flow.” INT.13.PPT.1 Trial PI & International Research Fellow

Although long-term trial partnerships were seen as important in helping to build this research platform, unlike in the Ethiopian case-study, Cameroonian participants considered the overall responsibility for its establishment to lie with national government. To encourage commitment from national decision-makers and achieve the investment required, participants said that greater advocacy was needed. They argued that decision-makers needed to be “sensitised” to research (FGD.2.PPT.2) and advocacy should focus on the importance and benefits of clinical research for the country. Seminars and workshops were reportedly an effective method of sensitisation.

5.5 Discussion

This chapter aimed to identify, understand and explain the barriers and enablers to locally-led clinical trials in Cameroon, and expand on the preliminary theoretical

framework proposed in the Ethiopian case-study by identifying similarities and differences in a similar research context.

The results have produced a thorough account of the issues faced by local trial personnel in Cameroon and once again demonstrate how multiple, inter-related, system-wide issues influence the conduct of locally-led trials. The findings from Cameroon complement those from the Ethiopian case study because many of the barriers and enablers to locally-led trials are common between the two countries and there are surprisingly few contradictions and divergences in opinions. However, the Cameroon case-study provided much greater detail on many issues which permits a more thorough understanding of how a research system can facilitate or impede the conduct of locally-led trials. This discussion will summarise key similarities and differences and explore additional details provided by Cameroonian participants.

5.5.1 Macro and institutional level influences on local trial undertaking

As demonstrated in the conceptual model of the Cameroon research system presented in section 5.4.4 (page 171), barriers to trial conduct were present at all levels of the research system and impacted on locally-led trial conduct in multiple ways and through feedback loops. These mechanisms were largely similar to those identified in the Ethiopian case-study. Clinical trial operations were also very similar, with the same key barriers at the start-up stage of trial conduct being reported as problematic. Although better funded foreign-led trials faced fewer barriers, their operations were still impeded by research system deficiencies.

In both countries, insufficient local funding and investment in research limited the scope of research that could be conducted. This made the conduct of clinical trials almost completely dependent on foreign funding, support or collaboration. However, while Ethiopian participants felt that supporting clinical trials was the responsibility of international actors, Cameroonian participants considered this to be the national government's responsibility. To get decision-makers to invest in research, advocacy of the importance and benefits of clinical research was needed.

Regulatory and ethical approvals were similarly problematic in both case-studies, for the same reasons. To overcome these issues, participants in both case studies considered capacity development of review boards and also researchers to be important. Positively, in both countries, there were initiatives working hard to achieve this.

Bureaucratic and complicated governance and disorganised stewardship were seen to impede the conduct of clinical trials in both countries. This was because they led to burdensome and time consuming administration and ineffectual targeting of research and implementation of policies. However, participants in Cameroon gave much greater details on the causes of this, attributing the problems to centralised hierarchical governance that led to the requirement for multiple permissions from multiple bodies and poor communication between these stakeholders. This organisational structure was regarded by Cameroonian participants to be an inherent part of Cameroonian culture that reportedly varied between linguistic regions, although this study found similar problems in both regions. Although respondents in Ethiopia did not attribute bureaucracy to centralised hierarchies, they are known to operate in Ethiopia [29 ,155].

Since decision-maker positions were mostly administrative, research expertise was not significant when appointments were made, meaning many decision-makers lacked appreciation for the research they were governing. This was strongly linked to low investment, low prioritisation of research-related tasks, suspicion and blocking of research, and inability of decision-makers to use research evidence. Without performance checks, low performance norms or obstructive practices could be perpetuated resulting in inefficient use of resources and operational bottlenecks. While these issues were most prevalent in public institutions in both countries, even trials that sought to bypass local systems still encountered problems because they often had to involve public institutions when applying for permissions or recruiting patients. The sometimes obstructive nature of decision-makers was not mentioned as deliberate in the Ethiopian case-study, but long delays due to low prioritisation of research were reported.

These arguments blaming organisational structures for inefficient operations are supported by literature that shows similar issues are common-place throughout Africa [28 ,151], particularly in post-colonial healthcare organisations where a lack of skilled staff necessitated strict supervision and adherence to protocols. This “machine-type” of organisation, with its powerful centralised command and control systems, are argued to cause excessive standardisation and focus on written records [247] that make them unresponsive to changing demands [152 ,153] and obstruct quality management [247]. Public-sector bureaucracy is also regarded as common throughout Africa and is thought to prevent effective use of resources [30 ,43 ,150]

To overcome administrative bottlenecks, Cameroonian participants made a number of suggestions, including streamlining procedures and providing fixed timelines to increase accountability of administrators. However, it was also clear that administrators and research support services required capacity development since they were often excluded from research development activities, especially by foreign-led trials who typically bypassed local administration systems. Furthermore, researchers needed to work harder to engage with decision makers and include them in research and its benefits. However, neither Cameroonian nor Ethiopian participants suggested clear strategies for improving relations between stakeholders. The Sri Lankan case study does provide suggestions for this, and these will be presented in the chapter 6 discussion (section 6.4.3 page 289) after the Sri Lankan findings have been presented.

In both Ethiopia and Cameroon, there was a clear demand for more clinical trials, especially locally-led trials, to provide locally-relevant evidence to tailor international recommendations. In Cameroon, local trial leadership was considered by some individuals to help facilitate this process. However, it was clear in both countries that this was rarely achieved. Findings from the Cameroonian case-study gave much greater details on this. Policy-makers often lacked capacity to use or commission evidence and centralised hierarchical organisation was seen to inhibit dissemination of research strategies and policies, discourage stakeholder engagement and communication between research-users and producers, and result in resistance to bottom-up suggestions to improve policy. This led to poor-relationships between researchers and policy-makers, and subordinates giving up trying to improve healthcare practices. Researchers failing to take initiative and

responsibility for national research was identified in the Ethiopian case-study, but was not directly attributed to centralised and hierarchical control.

However, it was also clear that researchers needed to produce more policy-useful research and make greater efforts at engaging with policy makers and disseminating their findings; even when policy-makers made an engagement platform to share research findings, this was not sufficiently used. As such, foreign-research was more often used for policy-making, not necessarily because the evidence was more useful, but because the greater resources, influence and credibility attached to foreign-evidence made policy implementation more possible.

Limitations in human and material resources inhibiting locally-led and foreign-led trial conduct were largely similar between the Ethiopian and Cameroonian case-studies. However, Cameroonian participants considered material resources to be more limiting than human resources, where as in Ethiopia the reverse was true. This appeared to be because Cameroonian participants perceived human resources with the potential to conduct clinical trials to be in existence, just ineffectually utilised. Conversely in Ethiopia, although skilled human resources were also being wasted, individuals with even basic research capabilities were considered lacking. While it is not clear if Cameroon actually had more research competent human resources or whether Cameroonian respondents were just more optimistic than their Ethiopian counterparts, ineffectual use of human resources did appear more problematic in Cameroon. This was because in Cameroon, counterproductive research cultures prevented the development and utilisation of human resources, in addition to the limited awareness, self-efficacy and motivation found in both countries.

In the Cameroon case-study, researchers were frequently viewed as professionally individualistic and competitive with their peers over leadership positions. Experiences of ideas and credit being stolen or research being sabotaged created a lack of trust, and senior academics failed to support and mentor juniors because they felt threatened by peer competition. Decision-makers also passed over expertise in favour of friends and political appointments. This led to a lack of communication and willingness to share ideas, made teamwork and cooperation difficult and mentorship and quality leadership less likely. This situation also made local networking rare which arguably prevented the positive impacts that local collaboration could bring. Although limited local collaboration and teamwork due to problematic professional relationships was reported in Ethiopia, this was not nearly as emphasised or seemingly severe as in Cameroon. Neither of the case-studies identified any strategies for overcoming these issues, but similar issues were reported in the Sri Lankan case-study and suggestions for improving relations were provided. These will be presented in the chapter 6 discussion (section 6.4.3 page 289).

5.5.2 Individual level issues influencing local trial undertaking

In addition to the macro and institutional issues mentioned previously, limited awareness, motivation and self-efficacy to lead trials were key individual level barriers to locally-led trial conduct in both Ethiopia and Cameroon. While the causes and consequences of these deficiencies in Ethiopia matched those in Cameroon, Cameroonian participants offered greater details on the importance of different incentives driving motivation and explanations of how self-efficacy could be

developed. These two concepts will be explored in more detail below, drawing from the psychology and organisational development literature to understand how these concepts may be shaped and may be amenable to change.

One of the most influential theories on work motivation [248] is the Motivation-hygiene theory, also known as Herzberg's two-factor theory of satisfaction and motivation [249]. This theory posits that there are two categories of factors controlling satisfaction; "Motivators" which give positive satisfaction and are needed to motivate employees to higher performance above their normal duty expectations, and "Hygiene factors" that do not give positive satisfaction but their presence prevents dissatisfaction. Motivators are intrinsic to the job itself and include elements such as: recognition, sense of achievement, personal growth, challenging work and opportunities for responsibility. Hygiene factors are extrinsic to the nature of the work and include: salary, promotion structures, supervisory practices and working conditions etc. This leads to the critical proposition that both hygiene factors and motivators must be present to motivate staff to higher levels of performance. Since conducting clinical trials in Ethiopia and Cameroon was seen as additional work beyond required duties in all institutions except dedicated research sites, undertaking clinical trials may be considered higher performance work, and thus would require hygiene factors and motivators for them to be attempted.

This theory appears to have strong traction with the motivational conditions reported in Cameroon and Ethiopia. This is because although recognition, career development, responsibility, challenging work and professional development were important, sufficient payment and improvements in working conditions were stated as essential for most participants to consider taking on extra research activities.

This was especially true for health workers because research was not recognised in their career progression. Although purely anecdotal, that dedicated research institutes had fewer problems retaining staff than other institutions suggests that their better working conditions resulted in higher staff satisfaction.

However, several participants from Cameroon said that salary and other extrinsic factors were not important, at least for a while, if strong motivators such as responsibility, ownership, recognition, learning, and challenging work were present. These factors were also important in the Ethiopian case-study for participants who conducted trials despite poor extrinsic incentives. This does not fit with Herzberg's theory. However, these differences are accommodated in later theories of motivation which state that individuals with stronger "growth need" (meaning a strong desire to take on more roles and responsibilities, master skills, and progress in their career) are more likely to respond positively to the following core dimensions of jobs: skill variety (a variety of skills are required), task identity (seeing a job through from beginning to end), task significance (understanding the importance of the work), autonomy (having control, responsibility and freedom in determining work flow), feedback (receiving direct information on effectiveness of personal performance) [248]. More recent business research has also demonstrated that noncash motivators including a chance to lead projects, are no less, or even more, motivating than the highest rated financial incentives [250]. These core job dimensions closely match the reasons that some participants preferred to work on and lead locally-led trials and explain why financial remuneration was not always essential. Therefore it appears that the respondents who conducted or wanted to

conduct locally-led trials, despite few extrinsic incentives, had higher than normal growth needs.

Self-efficacy is recognised as important for developing the “can do” mind-set required for undertaking and successfully completing jobs that involve expanded performance beyond routine duties [251]. Since conducting a locally-led trial was an expanded performance activity for most researchers, it is understandable why self-efficacy was so critical for locally-led trial conduct in both case-studies. Furthermore, self-efficacy has been theoretically linked and empirically demonstrated to be positively associated with behaviours that were important for successful trial leadership: persistence, reacting positively to setbacks, and negotiating and interpersonal skills [225 ,251 ,252]. Therefore, it appears that self-efficacy is not only important for having the confidence to undertake trials, but also the required behaviours, attitudes and performance to successfully achieve this.

Importantly, rather than being an innate element of personality, self-efficacy is conceived to be malleable. Bandura [253] theorised that self-efficacy is developed by four categories of experience: performance attainments (mastery through gradual accomplishments that develop skills, exposure and coping ability), vicarious experience of observing others (seeing others successfully deal with difficult situations), verbal persuasion or realistic encouragement (persuasive support and enthusiasm from peers) and physiological states (bodily responses to tasks such as arousal and fatigue). Others have shown that training can enhance self-efficacy especially if there are opportunities to enact technical mastery, see others successes [252] and develop inter-personal skills [251]. Greater job breadth, facing

new and challenging tasks, performance feedback [251], having responsibility for decisions and ownership of whole processes [248] have also been shown to increase self-efficacy. Autonomy and perceived control have been shown to be the most important determinants of self-efficacy [251], because “the more people believe that the causes of performance are uncontrollable, the lower and more resistant to change will be their self-efficacy [252]”. Extended exposure to low discretion jobs can therefore result in learned helplessness (essentially absent self-efficacy) [251] which can potentially be reversed by enhancing autonomy [254].

These theories once again closely match participant experiences in Cameroon and Ethiopia. Insufficient exposure to clinical trials led to misunderstandings that they had to be large complex studies, impossible to conduct without strong foreign support. Conversely greater exposure to clinical trials in daily practice, understanding they could be small manageable studies, and seeing successful examples of trials being done being done, increased investigators’ confidence. This is explained by the vicarious element of self-efficacy. Participant reporting that simple successful trial experiences and getting further training on research skills would increase self-efficacy tally with the performance attainment or mastery element of Banduras theory [253]. Reports of responsibility increasing confidence and maturity, and lack of control and ability to make a difference causing passivity, corroborate the argument that responsibility presents opportunities for reinforcing self-efficacy through mastery, but lack of autonomy and control causes helplessness. While participants did not say that lack of encouragement reduced their self-efficacy, they did say that support and enthusiasm for personal

development from managers was very inspirational, which links to the verbal persuasion element of self-efficacy theory.

While these findings and theories can never fully explain human behaviour, despite their universal perspective, they are important because they provide support for respondent arguments that organisational management practices used in public institutions, and foreign-led trials with limited local inclusion and leadership, did not support the mind-sets and behaviours required for local researchers to be able to lead their own trials.

This is because in public institutions, there was limited understanding of clinical trial significance and few opportunities to see trials successfully done, there were poor incentives, few learning opportunities, little encouragement and support, limited ability to take on responsibility and make a difference, and highly restrictive resources. When working on some short-term trial collaborations, highly formalised and simple protocol driven roles afforded few opportunities for learning, limited the variety of tasks that local researchers could be involved in, and there were few opportunities for responsibility, feedback and making contributions. As such these management practices were likely to significantly and negatively impact on self-efficacy [255], satisfaction, motivation and productivity [225] and result in employees that judge themselves to be lacking skills, tasks as overly complex and cause feelings of helplessness [251 ,256]. This is likely to explain why even investigators with foreign-led trial experience sometimes did not feel able to lead their own trial, and why researchers in Ethiopia reportedly failed to take initiative in conducting research.

Conversely, both participant reports and the aforementioned theories suggest that locally-led trials, and long-term trial partnerships that offer strong local leadership and inclusion, would more effectively build motivation and self-efficacy because they provide more opportunities for full involvement in the clinical trial from beginning to end, more chance to learn through overcoming challenging tasks, and more ownership, responsibility and ability to make contributions.

5.5.3 A suggested research platform to support locally-led clinical trials

When discussing the importance of a “research platform” as the ultimate package of sustainable enablers to research, participants stated most elements highlighted in the literature as important for system-wide health research capacity development: sufficient financing, material resources, institutional research support instruments, training, better incentives, and fostering a research culture through networking, research experiences, and recognition.

However, their assessments also extended to more subtle, intuitive and psychological driven understandings of how to develop locally-led clinical trial capacity, which were very similar to organisational development and psychological theory. Indeed their arguments and experiences of the need for research leaders and mentors to create effective teams and how staff and teams could be developed tick all the boxes for good staff management [257](pages 41-42): encouraging and supporting staff, making everyone feel valued and equal, encouraging communication and inclusion in decision making, professional development mentality, giving feedback and recognition, challenging employees, and giving opportunities to take responsibility and see whole processes through. Although it

was not clear from participant reports how these leadership skills were developed, additional participant reports from the Sri Lanka case-study allow suppositions to be made. These are presented in the chapter 6 discussion (section 6.4.3 page 291).

Networking and collaboration were undoubtedly important for getting research done. As was the case in Ethiopia, such collaboration was almost exclusively with foreign researchers because local teamwork and collaboration was uncommon due to relational and networking issues among researchers. However, participants emphasised that research outputs were not necessarily the sole or most important end result for them. For many the most highly valued outcome was the potential development for the research system, since getting research going and allowing people to be involved had a number of positive knock-on effects that could orientate employee behaviour and attitudes towards conducting their own trials: exposure to research, critical thinking, teamwork and cooperation, self-efficacy, motivation, creating a culture of excellence and raising professional standards, and creating research leaders. This lends strength to the argument that simple locally-led clinical trial experiences, if they are institutionally embedded, could have important long term benefits for the whole research system, not just individuals.

That embedding clinical trials in institutions is important for fostering these wider beneficial outcomes is supported by theories on experienced-based learning, situated learning and learning by doing [258], which have empirically shown to be critical in medical education [259]. This is because the process doing an activity, but also observing and participating with the actions of others helps develop communities of practice [241 ,260] (which research groups within institutions can be [182]). Interaction with these communities of practice then develops awareness,

motivation, self-efficacy, agency, and the ability to perform tasks and achieve goals, not only through direct experience but also through learning from peers and senior individuals. This is especially important for developing tacit knowledge that is not part of any curriculum but which can provide important knowledge on how to get things done. This would suggest that because locally-led trials are more commonly institutionally embedded than long-term trial partnerships, they may be more likely to develop these types of capacities. However, learning in communities of practice is affected by the community's readiness to engage learners and support their participation, so the negative team working attitudes and reluctance to support each other found in Cameroon may be a barrier to this. This lends further support for the need to develop supportive pro-research and team working research cultures.

Cameroon, like many countries in sub-Saharan Africa, is a long way from this ideal research platform. However, it is clear that progressive and successful progress is being made. Government efforts to address the absence of research incentives would appear to be very well founded and innovative new policy technologies designed to better integrate researcher users and producers are arguably a step ahead of many HICs. Improvement in ethical research conduct driven by increased attention to GCP and formidable improvements in ethical review capacity are also to be applauded. There are also indications that regulatory capacity and legal formalisation is improving. The national government was also developing the material capacity and infrastructure of several new and established universities, especially medical departments. Foreign collaborations and

partnerships have also made considerable improvements to local clinical trial capacity, both material and human.

However, locally-led trials in Cameroon still face considerable barriers that require both general improvements in the research system and specifically tailored considerations. In particular, it was clear that without greater availability of funds and resources for locally-led clinical trials, even investigators that had successfully conducted locally-led trials had difficulty sustainably doing this. This is problematic because it appeared that trial groups needed to conduct several clinical trials before they became sustainable. For the few local investigators that had achieved this, long-term foreign partnerships and support were essential. Participants suggested that the key to forming these quality relationships was being persistent and having good networking skills. However, although the above section suggests that self-efficacy is important for developing these behaviours, it was not clear how investigators fostered and sustained their supportive networks. This is considered in further detail in the chapter 6 discussion (section 6.4.3 page 289) because Sri Lankan participants provided greater detail on this aspect of research leadership.

5.5.4 Strengths, limitations and further work

The expanded scope of this research compared to the Ethiopian pilot has provided much greater detail on the barriers and enablers to locally-led trial conduct. Furthermore, there was strong congruence in the findings between the case-studies, which strengthens the analytical value of the theoretical framework and indicates transferability to similar settings. However, it is not yet known if the currently identified barriers and enablers and theoretical framework will be

applicable to dissimilar research contexts, or if other mechanisms influence trial conduct in different settings. A further case-study conducted in a broadly different research context would help ascertain this.

It may be assumed that a resource-limited country that more commonly conducts locally-led trials into different interventions, has stronger development indicators and is located in a different continent will have a sufficiently different research context to test the wider generalizability of the study findings. Furthermore, by comparing the findings from Cameroon and Ethiopia to a country that is more successful at conducting locally-led trials it may be possible to more clearly understand what factors facilitate their conduct. For these reasons, the final case-study was conducted in Sri Lanka.

Chapter 6: Lessons from locally-led clinical trials in Sri Lanka; testing transferability and capturing best practice

Investigator 1: *“The multi-centre trials, you learn about the paperwork and protocols, and the sort of protocols expected in other countries.”*

Investigator 2: *“And we learn things about terminology and to do a check list and the protocol as in the international trial SOP.”*

Investigator 1: *“But in a locally-led trial we learn different things I guess. We learn things on the ground. It is challenging and innovating because you always have to look for answers...the answer is not there in the protocol. So you need to be creative with how you look at things.”*

Process mapping exercise 4 – PIs of a locally-led clinical trial, Sri Lanka, 2013

6.1 Introduction

To assess if the findings from the Ethiopian and Cameroonian case-studies have wider generalisability, it was decided to conduct the final case study in a dissimilar research context where locally-led trials were more common. This was similar in design to the Cameroonian case-study, but by exploring influences on trial undertaking in a more productive research setting it was hoped that further enabling practices would be identified. This should both strengthen the analytical value of the

theoretical framework and also indicate which components, if any, are more broadly applicable. Where differences from the theoretical framework are found, it may also be possible to identify and explain the contextual factors driving the observed differences, thereby helping to refine the theoretical framework and potentially make it more widely useful.

6.1.1 Objectives

1. To identify, understand and explain the barriers and enablers to trial conduct in Sri Lanka, paying particular attention to locally-led clinical trials
2. To expand on the theoretical framework by developing a clearer understanding of how locally-led trials are facilitated, and considering which components may have wider generalisability and which are context-specific.

6.2 Study setting

Sri Lanka was selected as an interesting comparator to Cameroon and Ethiopia because despite also being a Lower Middle Income Country with resource constraints, it generally has better development indicators. It also conducts considerably more clinical trials, with a more balanced portfolio of intervention types, and the majority of trials are locally-led. For further information see section 3.3.3 of the methods chapter, page 91.

Research exercises took place in Sri Lanka between January and February 2013. Research was conducted in 4 areas: Colombo and surrounding region, Galle, Kandy, and Anuradhapura and the surrounding region. Colombo is the capital city and the commercial and research hub of the country with several universities and

major hospitals. Galle is the administrative capital of Southern Province and is the fourth largest city in Sri Lanka with a well-established medical school. Kandy is the second largest city in Sri Lanka and is an administrative hub with a long established and well respected university. Anuradhapura is the capital city of North Central Province and has a newly established university with a rapidly growing medical faculty. Although most cities and regions have their own universities, these areas capture a good proportion of the major universities in Sri Lanka, including the three most prolific publishing institutions [261], and some of the emerging ones. However, they are all limited to the Southern and North Central regions. This notably excludes Jaffna in the Northern Region which also has a well-established university and medical faculty [261]. However it was not possible to visit this region due to heightened security and limited time availability. Figure 6.1 shows a map of Sri Lanka detailing study locations. For further details of the study setting, please see section 6.3.2 of the results (page 235).

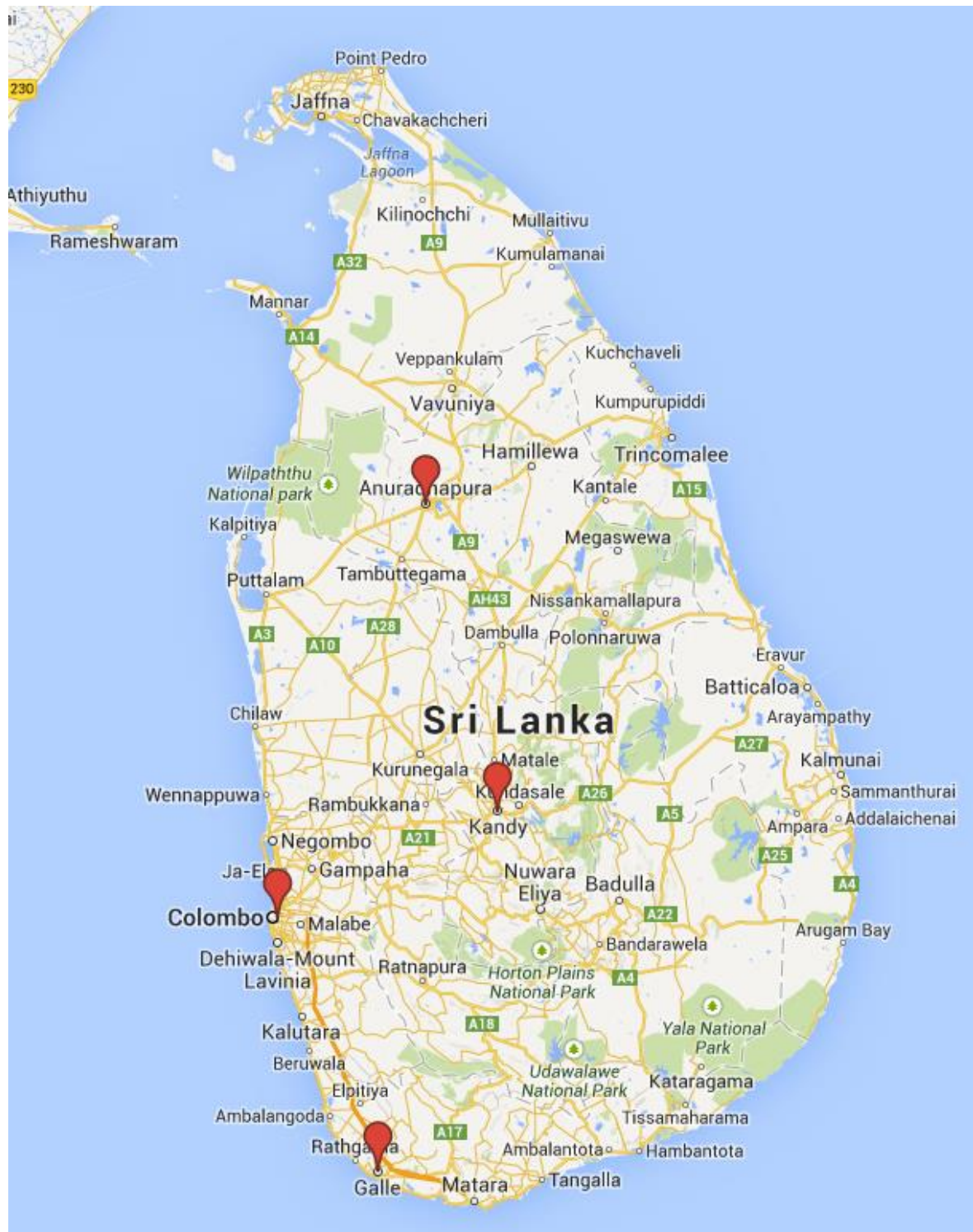


Figure 6-1 Map of Sri Lanka detailing study locations. Source Google Maps 2014 [239].

6.3 Results

6.3.1 Study population

Nineteen research exercises with 31 participants were conducted. Participants were recruited from: 6 universities, a medical research institute, 3 hospitals, a provincial health office, 2 government ministry departments, a regulatory agency, and a medical association. A breakdown of research exercises by type and location is provided in table 6.1.

Table 6-1 Research exercises completed by region

Research Exercise	Regional location				Total
	Colombo	Galle	Kandy	Anuradhapura	
Interview	8	1	0	3	12
Focus group discussion	3	0	1	0	4
Process mapping	1	0	1	1	3
Total	12	1	2	4	19

The participant's primary job roles included: academic (n=8), head of academic department (n=4), dean of academic faculty (n=1), research unit director (n=1), clinician (n=2), dentist (n=1) student (n=1) regulatory pharmacist (n=2), public health practitioner (n=2), project manager (n=3), laboratory manager (n=1), data manager (n=1), administrator (n=1), government ministry department director (n=2) and medical association chair (n=1). Despite these primary job roles, most participants had multiple professional responsibilities and diverse experiences. The professional experience domains covered by the 31 participants are shown in figure 6.2.

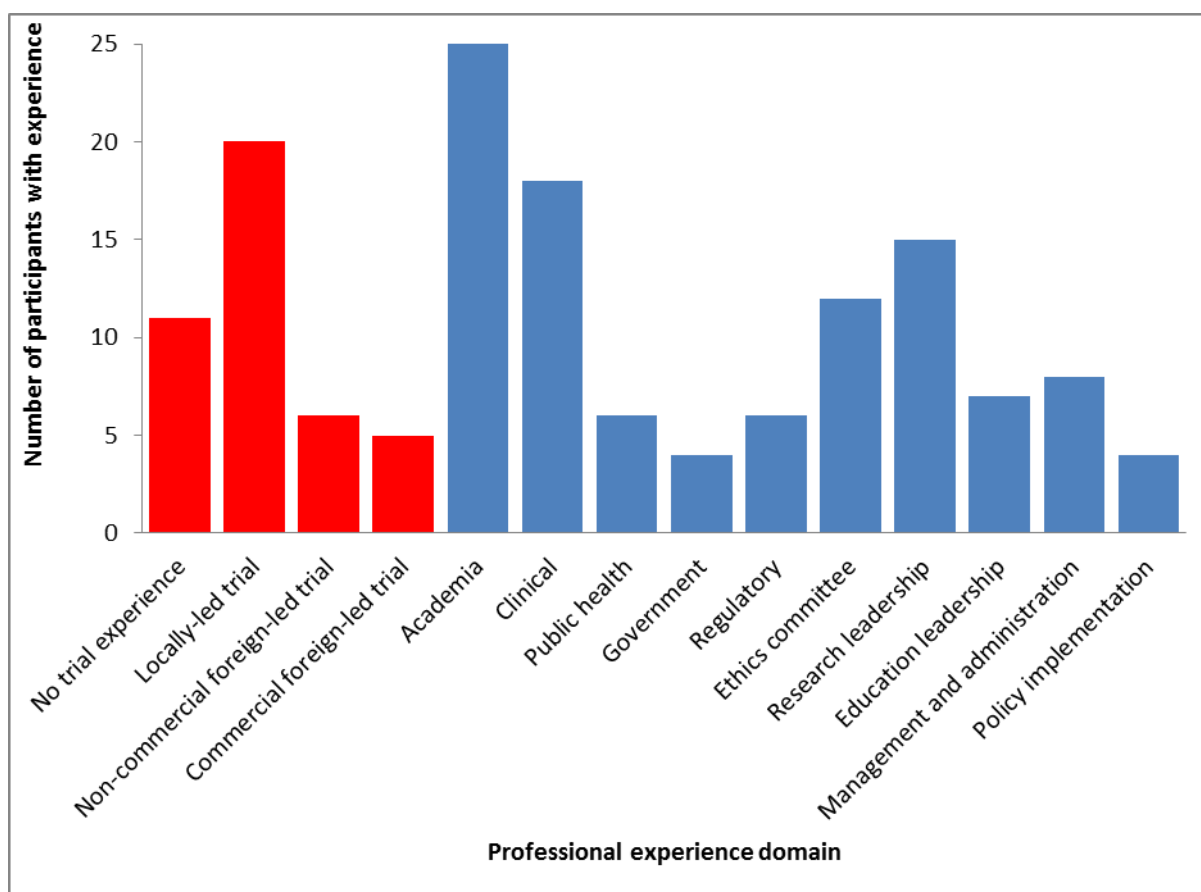


Figure 6-2 Professional experience domains of Sri Lankan participants. Experience domains are not mutually exclusive.

6.3.2 Research setting and context

Respondents all stated that most clinical research in Sri Lanka was descriptive, predominantly epidemiology, observational studies and baseline data collection. The reason attributed to this was that descriptive studies are cheap to conduct and finances for interventional studies are scarce. Clinical trials were viewed as one of the least common experimental methods, mostly due to the greater resources they required. This relative paucity of experimental research mirrors that of Ethiopia and Cameroon. However, unlike Cameroon and Ethiopia, the research

culture in Sri Lanka was viewed by participants as fairly vibrant, and indeed the absolute medical research outputs of Sri Lanka are higher than those of Cameroon and Ethiopia [261].

Where interventions were tested, these were typically comparative effectiveness of approved drugs, traditional and herbal medicine, and locally-important issues such as snakebite, poisoning and outbreaks of kidney disease. Participants all pointed out that locally-led trials rarely investigated novel product interventions because of their tendency to be resource intensive.

Of the clinical trials conducted, Sri Lankan participants were in agreement that most trials were locally-led. These were most commonly funded by local government grants and but some had commercial backing and support, often from local or regional companies. Foreign-led trials were reportedly much less common. Of the foreign-led trials, respondents explained that most were commercial studies and around 3 or 4 of these per year would be novel product trials. There were few examples of foreign-led non-commercial trials, either long or short-term. The exception to this was the trials run by a long-term international academic research network. However, rather than being foreign-led, this network was administered by Sri Lankans and had mixed foreign and local leadership. Therefore, although Sri Lanka was similar to the previous case-studies in terms of not investigating novel interventions and optimising the use of approved drugs, a much broader range of locally important topics were investigated through locally-led trials in Sri Lanka. Indeed the intervention portfolio of Sri Lanka appeared to mirror what respondents in Cameroon and Ethiopia thought should be conducted in their countries.

Regarding institutional productivity of clinical trials, participants reported that the vast majority of trials were conducted by medical and public health academic departments in universities, with a much fewer number conducted in hospitals and dedicated research institutes. It is worth noting that unlike in the previous case-studies, dedicated research institutes in Sri Lanka were almost always locally funded and embedded within the national research system. The only exception to this was the international research network because it received foreign funding. However, it too was locally-led and embedded within several research institutions within the country. Universities and academic researchers were generally much better resourced for research than hospitals and healthcare staff. However many academic departments had hospital associations and academic clinicians worked for both universities and hospitals, so delineating research outputs and resources between these institutions is difficult. Box 6.1 shows illustrative examples of clinical trial conduct in Sri Lanka.

Box 6-1 Illustrative examples of clinical trial conduct in Sri Lanka

Foreign and locally-led non-commercial trials in the international academic research network (FGD.12, INT.14, INT.17, INT.16):

This long established research network was created by local investigators and foreign academics to promote research on a particular neglected disease area. Funding was mostly obtained from large research donors. All research was carried out in Sri Lanka in various research sites throughout the country embedded in universities and academic departments of hospitals. These sites were administered and run by local staff and were well resourced with dedicated laboratories, IT facilities, administration departments and full-time staff. However, they were still strongly connected to their host institutions. This network had carried out a number of clinical trials and more were planned. The leadership of the trial depended on the individual project and the PI who initiated it, either local or foreign. However, local staff were always central to the studies. As such the network was more of a resource to be used by local or international academics to facilitate the conduct of their work. However local capacity development was also a key objective.

Locally-led trial in an academic department of a provincial hospital (PM.7):

This trial was run by a junior clinician as part of his medical academic studies and was funded through a government fellowship. This was a field based study in a rural area. The PI ran the trial by himself with some support from local clinic staff and the university supervisors. The provincial university and hospital that the PI was attached to lacked sufficient laboratory facilities to analyse samples so the PI had to make regular trips to the Colombo (over 8 hours away) to use facilities there. However, even then the scope of analysis was restricted. As such he was looking for an international partner to help analyse data. The trial had gone well and he would be interested in conducting another. However this would depend on funding and working conditions as he only did the first trial to get an academic qualification.

Locally-led trials in a metropolitan university (PM.4):

These trials were conducted in the medical faculty of a major university. The faculty was currently trying to form a trial support unit to encourage more clinical trials. However the trial unit was only made up of interested academics, some of whom had conducted trials abroad and could offer advice and support. It had no dedicated funding, facilities or full-time staff. To date this team had conducted 2 locally-led trials that were field-based. Local hospital laboratories were used rather than their university's facilities to avoid having to transport samples long distances. Funding for these studies was obtained from an international NGO. However, rather than being an open grant call, the funding was given based on the personal request of an international collaborator who the Sri Lankan trial team had previously worked with. This international collaborator was instrumental in encouraging them to attempt the trials and continued to provide support throughout, especially the design and publication. Having local trial expertise was also reportedly important for boosting their confidence. The trial group had several more trial projects planned.

6.3.3 Participant perceptions of clinical trials

Like in Ethiopia and Cameroon, Sri Lankan respondents said that there were many local evidence gaps that needed filling because international evidence was not always applicable to Sri Lanka. One good example was that of snakebite, where stark differences between the effectiveness of Indian derived anti-venom for treating Sri Lankan snakebite victims had been found. Like in the previous case-studies, trials were considered important for filling these evidence gaps because of the trial method's perceived superiority over other study designs. As such most participants said more local trials were needed, as this professor of pharmacology explains:

"...we always depend on evidence for our treatments, so clinical trials are the gold standard, that's the gold standard for efficacy in evidence. So therefore, I think we should try to do more clinical trials, particularly in areas where evidence is lacking." **INT.11.PPT.1**

However, like in Cameroon and Ethiopia, some Sri Lankan participants had concerns over patient safety and investigators' motivations. There were some reservations that local investigators may be more concerned with producing publications and academic recognition than patient benefit, while others thought that commercial companies were more concerned with profits than patient safety and community benefit. A clinical academic who was a locally-led trial PI explained this:

"But not all clinical trials are basically done to address, you know, what should be addressed in health sciences. It is driven by market or industry. So there's a good side of it yes, there are also, you know, sides which are not that fantastic as well. So, like what we just mentioned, clinical trials are not based on prevention. It's more for curative because there is a market there." **FGD8.PPT.1**

Participants' opinions on trials could be divided into 3 main categories of trial types. These were separated by study leadership and commercial orientation; foreign or locally-led commercial studies, foreign-led non-commercial studies and

locally-led non-commercial studies. Participant perceptions of these three categories of trials are summarised in table 6.2. While this table summarises the majority of views, not all participants agreed; some felt that trial leadership and commercial orientation did not matter as long as there was strong local inclusion, research was locally beneficial, and it was professionally conducted.

Overall Sri Lankan respondent opinions closely match those expressed by Ethiopian and Cameroonian participants. This includes the perception that locally-led trials would be more relevant and useful for policy and better at building sustainable capacity because they are embedded in the research system and develop independence and leadership skills; but also that locally-led trials had less scope, may be less professional and credible, and foreign-led trials may offer more material resources and better development of technical skills. However this was dependent on the level of local inclusion and dedication to capacity development. Sri Lankan respondents were generally more positive about commercial trials than previous case-study participants, although they were still concerned about local relevance and inclusion.

Table 6-2 Participant perspectives of trial characteristics based on differences in study leadership and commercial orientation

Trial characteristic	Trial type categorised by leadership		
	Locally-led non-commercial	Foreign-led non-commercial	Commercial
Scope and purpose	• More limited scope. Can compare approved interventions but not novel therapeutics. For this collaboration is needed • Useful for traditional medicine and disease management	• Wide scope especially when multi-national • Can be of broad benefit	• Wide scope especially when multi-national • Limited to products of commercial value
Professionalism and credibility	• May be of lower quality due to less expertise or fewer resources • Some argue local studies are less credible	• Professional and highly credible	• Highly professional and strong monitoring • Some suspicion of profitability bias damages credibility
Resource availability and operations	• Few resources available • Results in operational delays and difficulties	• Generally more resources • Easier operations than locally-led studies	• Lots of resources and support resulting in smooth operations
Local relevance and impact	• Highly relevant and can be used to change local policy	• Variable. Interventions may be locally relevant but normally less locally specific than locally-led studies • More relevant and greater impact if integrated with local research system	• Study topics may not fit local priorities and economic realities • Useful for getting local data on intervention effectiveness • Results may not be published
Trial ownership and local involvement	• Full local ownership and involvement in study	• Variable. Locals should be joint owners and have full involvement. However this is not always the case	• No local ownership & little involvement or control over protocol
Sharing of benefits	• Local investigators retain all benefits when independent, and most benefits when collaborative	• Variable depending on level of local partnership but generally foreigners retain greater proportion of benefit • Sometimes local staff only included for recruitment and given little recognition	• Local staff get little benefit beyond training • Economic benefit goes to government, and potentially useful for patients
Local capacity development	• More likely to develop local-led sustainable capacity as work within the research system • Problem-solving helps develop independence and leadership skills • However, often have lower budget, resource provision and less exposure to new techniques and standards	• Very good training provision, particularly monitoring and protocols. Provide material resources • Exposure to new methods, techniques and standards • Likely to result in less local leadership capacity as training generally more prescriptive but this depends on level of local involvement	• Lots of support, training on SOPS and GCP and practical experience, exposure to new methods, techniques and standards • Provide material resources • Less development of local leadership capacity as training prescriptive

6.3.4 Barriers to trial conduct

Although more locally-led trials were conducted in Sri Lanka than Ethiopia and Cameroon, participants still reported many system-wide barriers to trial conduct. Interestingly, many of the barriers and their drivers described by Sri Lankan participants were similar to those presented by participants in the previous case-studies. However, barriers reported in the Sri Lankan case-study appeared less severe and widespread. For instance, while healthcare institutions and clinical staff in Sri Lanka faced many of the same barriers as in Ethiopia and Cameroon, universities appeared to provide a fairly conducive research environment for academics. Although this was also true of some institutions in Ethiopia and Cameroon, adequate capacity or enabling mechanisms were far less common.

A conceptual model detailing research system influences on locally-led trial undertaking in Sri Lanka is shown in figure 6.3. This diagram mainly focuses on the barriers to trial conduct and their operations. However, this model also attempts to reflect the diversity of participant experiences with the research system. Where barriers are not mentioned as problematic for particular groups, this means they experienced few issues with that component of the research system.

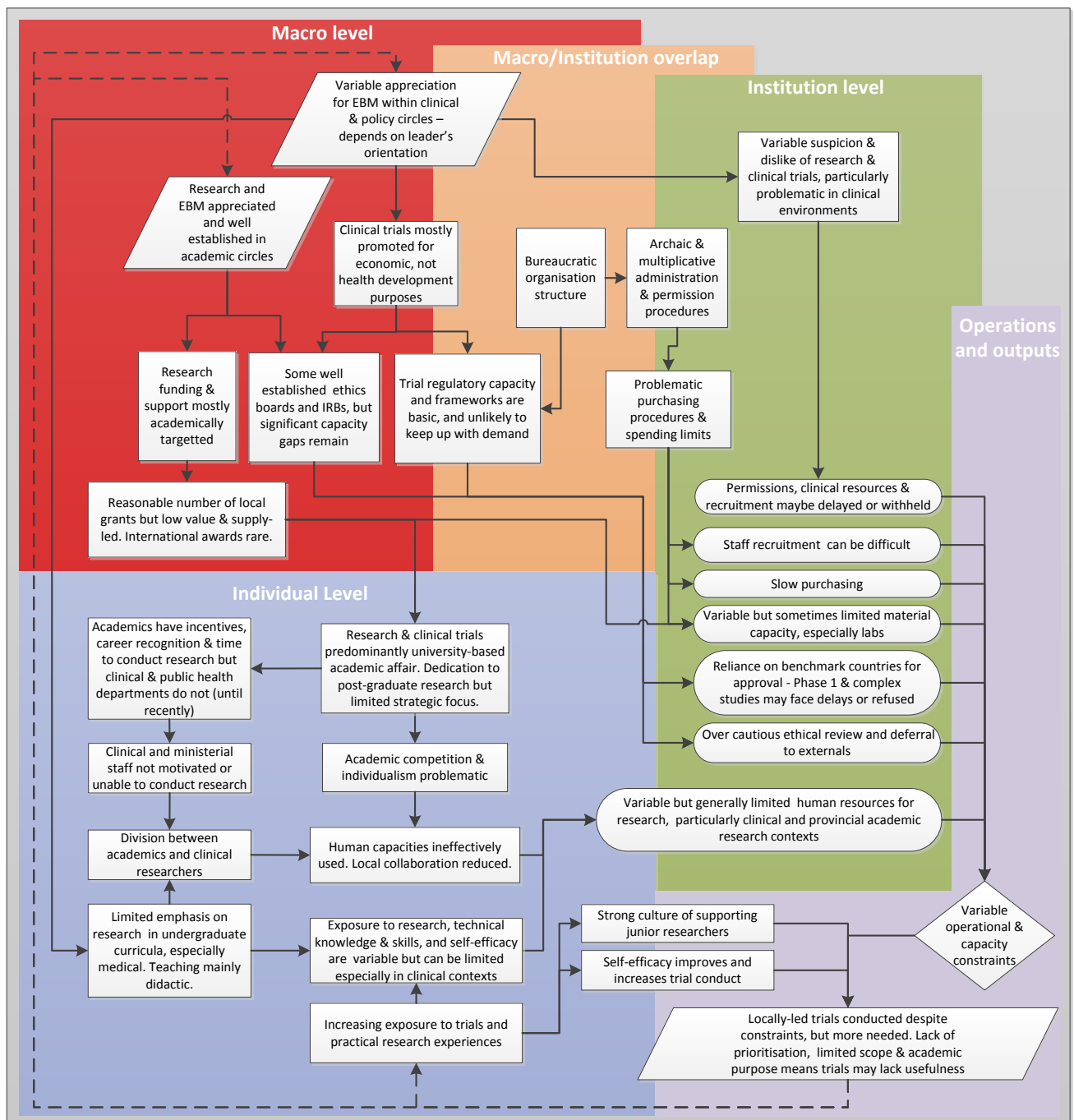


Figure 6-3 Conceptual model of the Sri Lankan research system, detailing barriers to locally-led trial conduct and their downstream effects.

Parallelograms represent the start and end of processes. Dashed lines show feedback loops. Note: hypothetical enablers are not included and not all barriers may be simultaneously present.

6.3.4.1 Research governance and administration

Governance and administration in Sri Lankan institutions apparently faced similar problems to those described in Ethiopia and Cameroon because they were also structured according to centralised, bureaucratic hierarchies. Like in previous case-studies, Sri Lankan participants said this imposed layers of bureaucracy which slowed research processes. As also suggested by Cameroonian participants, some Sri Lankan respondents felt that hierarchies segregated the workforce and encouraged competition through the demonstration of superiority, as this clinical professor explained:

“The second problem we have is that we have a very hierarchical system. It’s amazing how [Sri Lankan] doctors who trained in the UK would adjust to that system and show absolute dignity to everybody else, but come here and insist on being the top of the pyramid”.
INT19.PPT1

This was especially problematic where permissions were concerned because when decision-makers did not consider research to be a high priority, lacked appreciation for research, or disliked working with researchers, they delayed research or were deliberately obstructive.

However, governance attitudes towards research varied considerably between institutions and individual leaders. Healthcare institutions reportedly often had a negative attitude towards research, with staff sometimes treating research with suspicion, not considering research an important activity, and deliberately making research difficult, as this academic clinician explained:

“There are many people, medical professionals, they sort of, try to stop the project. That has happened because they don’t recognise the importance of our study and also they don’t recognise the importance of the roles of the other professionals.” **INT.17.PPT.1**

This negative attitude towards research was reportedly partly due to lack of incentives for healthcare staff to conduct research. However, clinical researchers also explained that doctors who did conduct research were considered a threat to the status quo. The reported driver of this situation was a dislike for evidence-based practice. Therefore research was not seen as important and it could potentially lead to standard treatment guidelines that would compromise clinicians' autonomy. However, some doctors pointed out that research was not valued because it was mostly academic and not practically useful. A public health researcher explained his experience with purely medical personnel:

"So they think they know what they are doing, so they say "They can't change my practice. I'm having my own practice". These dengue and maternal health guidelines have been developed and people don't want to take part in the investigation procedures because they know they have not been following the relevant guidelines, so now they are against the management guidelines... So they think that by engaging with clinical trials this will make their situation worse." INT.18.PPT.1

This attitude was also reported to be prevalent within ministry systems because managers were portrayed as sometimes lacking capacity to understand research due to non-meritocratic political appointments, and being concerned that research could be used to show up their failings. However, these attitudes were far from universal because receptiveness to research reportedly depended on the individual in charge, and some leaders were very enthusiastic about research.

However, within academia, few problems with research permissions or negative attitudes towards research were reported. This strongly contrasts with the Ethiopian and Cameroonian case-studies. This was reportedly because Sri Lankan universities all had strong research cultures and actively supported research activities, especially when they were conducted by junior researchers as part of their

academic studies. This was attributed to research being a required activity for academics and essential for career progression.

Regardless of decision-makers attitudes towards research, administration was frequently cited as a major impediment to research. Although most problematic examples came from universities, participants said this situation also applied to healthcare and government institutions. The issues experienced and solutions suggested in Sri Lanka closely matched those raised in the Ethiopian and Cameroonian case-studies. However poor work cultures and corruption were not reported in Sri Lanka.

Strict and time-consuming procedures had to be followed for even the most minor actions. Furthermore, governance policies were reportedly outdated, added little value, penalised researchers, and could make research unfeasible. Purchasing systems were once again regarded as particularly problematic. Despite having funding available, meagre spending limits reportedly prevented PIs from purchasing more expensive but better quality equipment, hiring research staff, claiming reasonable expenses, and offering sufficient remuneration to attract staff. Impractical tendering requirements and slow fund disbursement often delayed projects and could significantly impact on project timelines. In one example a major equipment purchase had taken more than a year, significantly delaying the start of a research project. Even small repeat purchases such as test kits were not exempt from these requirements, meaning tendering procedures had to be carried out for each order. The PI of a commercial trial explained his experience of tendering procedures:

“It [procurement] is handled by the bursars, but then we have to give all the specifications, they have to put a paper advertisement asking people to call, send in their quotations. Then that will have to be approved by a major procurement committee – so you have to wait until the committees meet. I think they meet about once a month, but then if some of the members are not there, things get delayed, and so on.” INT.11.PPT1.

Like in Ethiopia and Cameroon, several Sri Lankan participants highlighted that most universities do not have a research support service and administration departments were often under-resourced. Administrators said this was because research services were not recognised as important and they rarely received any investment or specific budget allocation. As also found in the Ethiopian and Cameroonian case-studies, budget planning in grant applications was nearly always done by the principal investigator with little involvement of administration staff. Participants explained this meant PIs commonly forgot to add in a budget line to employ an administrator, even when this was allowed within the grant, and they were also unaware that more favourable conditions for purchasing and procurement could be written into the grant. Careful planning and early engagement with administrators, as well as the ability to negotiate better contractual terms, appeared to be an important enabling factor. The head of a clinical and academic department explained this:

“So if you are going through the correct parties [administration department] I think it’s not difficult. If you prepare early, especially when you are getting documents signed at the grant writing stage, if you clearly mention “I’m not going to adhere to this. Within this timeframe I can’t do it. This is how we are going to do it”. So we don’t get all these administrative problems. But if you don’t do that, at the grant writing budget stage, then you will have problems of going through all these administrative procedures..... But you have to say all of this within the time limits. If you don’t, then you can’t spend your money. That is what happens.” INT18.PPT1.

Citing good practice examples of when they had worked on international studies within Sri Lanka, other participants argued that many of the bottlenecks

could be removed if procedures were updated and streamlined, accountability and timelines made clearer, and researchers given greater autonomy to manage more minor responsibilities themselves. The following quote shows how similar administration experiences in Sri Lanka were to the previous case studies:

“[In international collaborative studies] all the purchases and small expenditures, we were given guidelines and we could decide on our own. Our large purchasing, we needed only one approval.. But when it comes to the national [local institution studies], the immediate supervisor should approve, then the grant coordinator and there are so many steps. You have to wait to get approval, even for very small purchases, so it takes time...Even for paying for stationary we have to get a lot of approvals... In International funding the guidelines and time targets are very clear, there are not delays and if there is a delay there is clearly someone who is responsible. But when it comes to the national [local institution study], I don’t see a clear responsibility holder.” **FGD12.PPT.3. Project manager**

As such, several participants thought that dedicated research support units would be very helpful for increasing research productivity. However, like in Ethiopia and Cameroon, there were no examples of dedicated research support services outside of foreign collaborations, and while these international studies succeeded in improving administration, they did so by bypassing local systems. According to one respondent this meant local institutions did not receive overheads and thus missed out on opportunities for capacity development.

6.3.4.2 Research stewardship, investment, and uptake

Many participants reported that clinical trials and clinical research in general had gained increasing value in government circles over the past few years. This initiative, rather than coming from the Ministry of Health, had been driven by economic interests from the treasury departments. Their vision was reportedly that Sri Lanka should become a scientific and technical hub for South Asia, in the image of Singapore and Malaysia. As part of this vision, clinical trials were being promoted

to boost economic growth through attracting pharmaceutical investment. Foreign commercial studies were also encouraged to fill the current capacity gap for conducting trials of novel therapeutics. The government's goal was that these studies would strengthen local capacity so that eventually Sri Lanka could develop its own pharmaceutical and R&D industry. A regulatory pharmacist explained this by saying:

“They think they can attract foreign revenue here. That’s the treasury side. Also the other thing is that at the moment we don’t have the ability to conduct big research here, that’s the funding and facilities we don’t have, so it is better to have some international research.... then if we initiate the international multi-centre trials here at least, then one day, through capacity building, we can do our own thing better than today.” FGD.6.PPT.1

Although increasing recognition of clinical research importance was also reported in Ethiopia and Cameroon, in Sri Lanka support for clinical research was more practically implemented, had more top-level buy-in behind it, and was focused on commercial trial activity. However, the Ministry of Health was reported to have little interest in clinical trial research, preferring to focus on clinical service provision, so it was clear that this vision for clinical trials did not have universal buy-in.

One of the ways support for clinical research and capacity building was demonstrated was by the number of local funding bodies and research support associations. These included: The National Science Foundation, The National Research Council, The Sri Lankan Medical Association, and individual ministerial and university grants and bodies. In addition to research project grants, salary incentives for doctors to undertake research had recently been introduced to combat the lack of healthcare research culture.

While these investments appeared successful in creating interest in research and stimulating local research outputs, the limited financial value was said to restrict the scope of research that could be attempted. Therefore, despite national investment efforts, funding shortages for more ambitious research remained a perennial problem. This situation, combined with difficulty gaining funds from international donors, was why attracting international studies had become a preferred strategy for securing investment and capacity development, as this director of a ministerial department explained:

“Financing is the problem and there are issues with [local] donor funding. [International] Donors won’t fund us for doing research, so we want to develop and attract international research so they can help us get funding and we can learn technical skills from them and get exposure and learn from them. This could be commercial or non-commercial [research], as long as it’s ethical it doesn’t matter.” INT10.PPT.1

Many participants also explained that research grants were sometimes ineffective at targeting research towards priority areas because there was a lack of focus on priority disease areas. Although specific research gaps were mentioned by participants, there appeared to be no widely known official strategy or priority list. This meant that research was normally investigator-driven, not demand-driven. The exception to this, where there had been a great deal of targeting, was an outbreak of kidney disease of unknown aetiology. A ministerial director explained this:

“There are no bodies that identify research gaps then ask for research. We have National Research Council-like bodies that will put out calls for research funding. But they don’t identify the research questions and then ask for research on this– they ask researchers to submit proposals, then they will fund it.” INT.9.PPT.1

Participants frequently said that this led to academic investigators gaining grants to undertake irrelevant or duplicative work purely for career progression, or doctors seeing research incentives as automatic salary top-ups rather than a reward for

impactful outputs. As such the research outputs were largely academic or token efforts, as this senior academic explained:

“Currently we just do ad hoc research, you know, whatever takes our fancy. Most research is not useful and done individually so it is fragmented so we can’t make recommendations based on these individual studies. We need a coordinated and strategic approach but there are no priority areas. The Ministry of Health should be doing this but they don’t.” INT3.PPT1

Given the gaps in clinical evidence, sometimes limited usefulness of research, and variable responsiveness to evidence-based practice, participants reported that most clinical practices were not based on solid evidence. In some cases, even where good evidence had been generated, investigators still had difficulty influencing treatment guidelines. As such, standard treatment guidelines for some conditions were absent and treatment remained subjective. However, other participants argued that good quality evidence was usually well received by policy makers and gave examples where guidelines had been successfully changed based on locally generated evidence e.g. antibiotic use and treatment for poisoning. A public health practitioner explained that evidence uptake really depended on the attitudes of individual programme managers, while a Ministry Of Health worker noted that lower level policymakers were generally more enthusiastic about research but at higher levels there was less interest in evidence and more political consideration. Therefore the uptake of evidence appeared dependent on the policy programme, as explained by this public health researcher:

“Some programmes like malaria programmes, they use evidence and some programmes in communicable diseases, some of those aspects are evidence-based, some it’s not. It basically depends on the person. Some programme managers are using the lowest level of evidence, expert opinion.” INT18.PPT.1

Therefore, although there was much greater local investment and top-level support for clinical research in Sri Lanka compared to Ethiopia and Cameroon, funding constraints and poor targeting of research still resulted in local research of questionable value and impact on policy. However, that local research had influenced policies and investigators were engaging with policymakers shows that, on the whole, Sri Lanka was more accomplished at local evidence utilisation than Ethiopia and Cameroon.

6.3.4.3 Research regulation

Government regulators pointed out that if Sri Lanka wanted to encourage pharmaceutical investment and increase trial conduct, both regulatory and ethics review systems needed to be strengthened.

Participants reported that there had been important recent successes, such as forming the Sri Lankan Clinical Trials Registry, committees on clinical trials, training of ethics boards and getting 8 review committees recognised by the WHO Strategic Initiative for Developing Capacity in Ethical Review. However, most of these successes only related to ethical review and were attributed to actions of interested volunteers, rather than government commitments. Where official involvement was required to create legislation and improve regulatory procedures, the process was reportedly delayed by an apparent lack of interest, as the chair of a medical association explains:

“It has taken ages to get the clinical trials act [through parliament] and it keeps going backwards and forwards and many of us don’t know what the problem is. So we have made it very clear. We can try [to build governance capacity] but we need money to pay our staff, and they need money to establish ethics committees and their offices... What is happening now is very much the personal involvement of researchers and university staff doing the

best they can with the resources they have. It's fair to say that unless there is a lot more interest and input from government sources, it's not going to take off. We have been trying to point out the necessity of having legislation to make legal backing to ERCs. But there is no interest [from the government] in trying to get that." **INT2.PPT.1**

This had reportedly left significant gaps in regulatory capacity, slowing government approvals required for trial conduct. In particular, participants noted that there were almost no regulations on clinical trials so approvals often just followed those of benchmark countries e.g. MHRA in the UK. Furthermore phase 1 trials were not normally allowed because the regulatory agency felt they lacked adequate expertise and legal frameworks to review them. This made it very difficult to get approval for testing novel drugs. Aside from the lack of legislation, participants also explained that regulatory staff were under-resourced, had heavy workloads, were often inexperienced and lacked access to training particularly in protocol evaluation and GCP monitoring.

Furthermore, despite improvements in ethical review capacity several participants said that ethics boards still lacked capacity and expertise to cope with complex clinical trials. This lack of confidence in monitoring and review capacity, combined with fears of unethical practices, appeared to fuel nervousness about clinical trials. Participants argued that this caused ethics boards and institutional decision-makers to be often over-cautious, meaning trial investigators sometimes had a great deal of trouble convincing them to permit their studies. A pharmacology professor who had led several trials explained this:

"And then if there are sort of any prominent members who are really cautious, then the whole committee tends to go along with that, because of the lack of expertise, and so it took some time with other experts before it could be approved." **INT11.PPT.1.**

Therefore, although Sri Lanka had more advanced ethical review capacity than Ethiopia and Cameroon, similar problems were still experienced, and regulatory frameworks appeared comparably underdeveloped.

Despite these issues, it was clear that progress was being made, and not just in ethical review. The Cosmetics Devices and Drugs Regulatory Authority only began regulating clinical trials in 2009 and regulators provided clear details of plans for expansion, including creating a dedicated Clinical Trial Authority, strengthening regulations, developing SOPs and building human resource capacities. Participants were hopeful that once legislation was passed, regulatory investment would shortly follow and capacity would increase.

6.3.4.4 Human resources availability and development

Sri Lankan participants reported similar human resource shortages and skills gaps to those mentioned in Ethiopia and Cameroon. However, in general, reported problems with human resource availability for research were not as severe as those experienced in the previous case-studies, especially Ethiopia. The exception to this in Sri Lanka was in more rural areas and provincial universities because institutions had difficulty attracting and retaining quality staff. The head of a public health department in a smaller provincial university explained his situation:

“I need research staff who can understand research and who can implement research, so that is a problem here now, even if I advertise for research assistants, it’s difficult to get people who understand research.” INT.18.PPT.1

Designing trials, laboratory, data management, statistics and publication skills were in particularly short supply, with several participants saying they had difficulty analysing their data and really needed data experts to consult when designing

studies and writing publications. One locally-led trial team in a prominent university had recruited a statistician from a mathematical department but this led to difficulties because she was not familiar with medical statistics and when errors occurred the trial team lacked sufficient knowledge to notice the mistake.

Many Sri Lankan participants thought that the key driver of the shortage of research expertise was the minimal inclusion of research within medical education. Several participants suggested that more research modules, particularly clinical trials should be added. Others argued that research modules needed to be more practical. A medical association chair explained this:

“Well it’s a question of trying to get people away from just learning from books and the notes and then just reproducing it in exams. Because this is a problem that we have actually, in that learning is very much a didactic process...So the idea of getting them to do a research project, is trying to increase independent thought and initiative.” **INT2.PPT.1**

A key barrier to these suggestions was that educators in less established universities felt they lacked sufficient resources and research competent lecturers to be able to effectively teach research. Other lecturers said they would face resistance if they tried to make research a more important component of clinical training because medical education leaders often lacked appreciation for research. However, there were successful examples where community-based research projects and research electives had been incorporated into curricula.

While the limited availability of research teaching was more problematic for clinical professionals than other biomedical fields, researchers from all professions said that teaching and training on clinical trials was scarce. As such, many researchers said they had to develop their knowledge of clinical trials through informal channels and self-directed learning. To develop further human resources

for clinical trials more formal courses, workshops and e-learning resources were reportedly needed. However, some senior educators suggested that mentoring by experienced trial staff could be very helpful and such support could be found if requested. Indeed, one junior doctor doing a clinical trial for his PhD said that the mentorship he had received had been critical to the success of his work. He explained that in Sri Lankan medical culture, people were usually very supportive of research students, so if there were difficulties accessing mentorship it is likely due to inadequate time, rather than disinterest. Therefore, although the Sri Lankan research system faced similar shortages of clinical trial training as the Ethiopian and Cameroonian research systems, the greater number of trial experienced personnel in established universities and more supportive research cultures appeared helpful in moderating this problem.

Like in the previous case-studies, Sri Lankans thought that practical experience was essential for learning trial skills and abilities because only through hands-on involvement did investigators reportedly feel confident to begin leading their own trials. However, unlike in Ethiopia and Cameroon, few Sri Lankan participants said practical trial opportunities were limited. There were reportedly excellent government funded fellowships for doctors to train in high-income countries, particularly the UK and Australia, but the high cost meant that few places were available. Therefore most respondents said their formative trial experiences were working as staff on locally-led and commercial studies. Commercial studies were reported by some participants to be a particularly valuable early trial experience because they provided exposure to new methods and more rigorous procedures, as the current PI of a locally-led trial explained:

“I don’t think that you have the confidence to at once design a trial on your own by just reading things, or just getting GCP training. You have to get involved in trials, and actually, my conduct of academic studies improved after I participated in commercially funded trials... You see, some of the things we were doing with academic studies, we were not adhering to some things that we should have. Participating in commercial studies improved my conduct.” INT.11.PPT.1

However, while some respondents said that they could learn most effectively on foreign-led trials due to easier access to resources and greater exposure to expertise and monitoring practices, other participants disagreed. This was reportedly because foreign-led studies only taught specific technical skills, tasks were strictly procedural, protocols and SOPs were already prepared, and local researchers often just had to follow orders. As a result, Sri Lankan respondents explained that foreign-led trials were only useful for developing more junior levels of expertise. Conversely, when working on a locally-led trial, investigators said they were forced to work through complex senior management elements themselves and this responsibility and independent learning process was critical for developing the knowledge, self-efficacy and motivation required to develop their leadership expertise. Participants who were more interested in working on commercial studies tended to be junior, and those who preferred to work on locally-led trials were more senior. These experiences of trial learning and preference for different trials closely match those described in the previous case-studies, especially Cameroon, which supports the supposition that preference for different learning scenarios is linked to the career stage the individual is trying to develop. Two senior local trial investigators who had worked on both foreign and locally-led trials explained the difference in learning opportunities between these 2 types of trials:

PPT1: “The multi-centre trials, you learn about the paperwork and protocols, and the sort of protocols expected in other countries.”

PPT2: “And we learn things about terminology and to do a check list and the protocol as in the international trial SOP.”

PPT1: “But in a locally-led trial we learn different things I guess. We learn things on the ground. It is challenging and innovating because you always have to look for answers...the answer is not there in the protocol. So you need to be creative with how you look at things.”

PPT2: “In the multicentre trial, everything is done for you, everything has been taught. You don’t need to worry who is making the placebo and whether the placebo will look like the drug and that kind of stuff.”

PPT1: “So I don’t find those multi-centre trials as interesting as this [their locally-led trial]. We still have a tremendous amount of achievement after having, you know, having done all this and shown it to you.” **PM4.**

6.3.4.5 Effectively leveraging human capacity

As found in the previous case-studies, the manpower shortages for research in Sri Lanka were not just attributed to lack of expertise. Like in Ethiopia and Cameroon, lack of time and motivation to conduct trials reportedly greatly reduced the pool of investigators who were willing and able to conduct trials. Lack of awareness and self-efficacy to conduct trials was also reported. However this was much less commonly cited as problematic in Sri Lanka compared to Ethiopia and Cameroon. Furthermore, these issues were only considered problematic in healthcare organisations and some ministry departments, reportedly because they lacked research cultures and therefore there was little exposure to trials. The lack of research culture in these organisations was linked back to insufficient time and motivation to conduct research.

Lack of time for research was a major problem for clinician researchers and some ministry personnel, with some of them ranking it as one of top barriers to research. The reasons for this were the same as in the Ethiopian and Cameroonian case-studies. Although time was rarely cited as a major barrier to research for full-

time academics, it was problematic for researchers in smaller universities due to general manpower shortages. Box 6.2 shows selected quotations on time availability for research.

Box 6-2 Participants reporting lack of time for research

"You need dedicated time off for research, time off from the clinic and teaching. This is not available. We have some good training and patients and some materials – the issue preventing research is time and finances." INT.3.PPT.1 Clinician and academic

"But to write a project proposal, you have to have time, and maybe that is what the clinicians do not have. But in our case [academic] we have time." FGD.8.PPT.2 Academic, non-clinician

"So you see to sit down and do some research work, its very difficult. I'm currently the head of this department, so I have teaching commitments, administrative commitments, I have clinical commitments, I have my research commitments and I'm supervising PhD students, so in all of that the aspect which gets worse affected is my research and particularly publication." INT.11.PPT.1 Clinician and academic department head

One of the most common and reportedly effective ways of releasing capacity to conduct research was simply by hiring a research assistant or staff to cover overburdened researcher's routine duties. However, meagre institutional spending limits, short term contracts, and low salary rates reportedly made it hard to attract and retain staff. If extra staff could not be organised or leave from regular duties was unavailable, taking on a clinical trial would be a lot of extra work, and for this potential trial investigators needed suitable incentives to motivate them, as explained by this academic clinician:

"There has to be an incentive if a clinician takes up clinical trials, because its really, really difficult because there is no time, basically to manage it with your normal tasks. Taking on a clinical trial is a lot of time, a lot of work. However, having somebody else, you know, who will run it for you. That is one option. That is one solution." FGD.8.PPT.1

Like in the previous case-studies, the need for better incentives was particularly important for clinicians. This was because healthcare workers did not normally have salaried research time so research would have to be conducted in personal hours and this would cut into private medical practice resulting in salary loss. Also like in Ethiopia and Cameroon, conducting research did not significantly impact on medical career progression since promotion was mostly based on time served. Furthermore, clinicians sometimes faced criticism for conducting research because they were breaking the status quo. As such, physicians had little motivation to conduct research and were largely unreceptive to efforts to involve them in clinical trials. For ministry staff, research was potentially part of their job description but it came well below service provision and teaching as a priority. However, unlike the previous case-studies, full-time academics were highly motivated to conduct research because it was essential for career progression and they had salaried time allotted for research.

However, all participants regardless of professional group said that frustrations with lack of resources and difficult institutional procedures were disincentives to conducting research. This was especially true for clinical trials because they were considered more of a hassle than other types of research. Indeed one locally-led trial PI who was a clinical academic said that he would not be keen to conduct another trial unless there were more favourable working conditions and he only did the first trial to get an academic qualification. Box 6.3 shows common opinions on motivation to conduct research:

Box 6-3 Participant opinions on motivation to conduct research for academic, clinical and ministry staff

“There are people who do research and there are clinicians who do research, but getting into a trial, because it involves a lot of work, it’s not a thing you would go after”.

FGD.8.PPT.1 Consultant physician and PI of a locally-led trial

“Lots of consultants are engaged in working outside their working hours in private practice. So, I don’t think they have enough time to consult for research. They are fully engaged in the hospital and even after that, another five or six hours, some people work in the private sector, otherwise they can’t maybe, maintain their status or whatever. So, I mean, those are the realities. I don’t think they are correct or whatever, but, as a result, the research comes last in their priorities. But at universities it’s different with incentives. Unless you do research you can’t go up the ladder. But the others who work for the Ministry [of Health] just want to work and that’s all.” **FGD.5.PPT.2. Consultant doctor and undergraduate lecturer**

“Research is restricted to academic individuals. Doctors who are not academic do not get any benefit in money or recognition and career development for doing research. Research is not appreciated as part of career development by the Ministry of Health.”

INT.14.PPT.1 Academic, clinician and trials unit director

“If you want to become an important consultant, then you may have to do some research, otherwise if you just want to be a class one medical officer in eighteen years’ time, then you don’t need research to go up. So it’s sort of a forgotten area, and to do research, you are looked like a person with a small stigma attached.” **FGD.5.PPT.1 Government public health practitioner**

These differences in rewards and incentives for conducting research also reportedly caused relational problems between academics and healthcare workers which prevented local collaboration and made research in clinical environments difficult. The main areas of disagreement were reportedly over the sharing of workload and benefits. University academics felt that clinician researchers demanded too great a share of the recognition when contributing little to the study except access to patients. Conversely clinicians felt their contribution was sufficient

considering that they received few incentives for conducting research. The following quotation is a discussion between a clinician researcher and a medical academic:

PPT1-Academic: *“We have to get the help of the clinicians if we want to put out something that is benefiting the country. But we know the clinicians do the least amount of work. For example, I did a study on hypoglycaemia. The only contribution that the clinician made was the sample. We did everything else. I guess we need to accept that clinicians cannot contribute as much.”*

PPT2 –Clinician: *“Clinicians do not have much time for research but actually clinicians do do research. It’s just not for PhDs and career progression. If you really read through the medical output, you would see there is a lot of research being done.”*

PPT1-Academic: *“That is not being done all over the place. None of you collaborate. That is what I find.”* **FGD8**

As such, this situation was very similar to the relational issues between academics and clinicians reported in Ethiopia. In recognition of the lack of research incentives for clinicians, the government had recently introduced salary top-ups worth 25% of clinician’s basic salary if they undertook biomedical research; continuation of this benefit was contingent on publishing. Most participants agreed that this was a very positive step and it had increased clinical research. However financial rewards were not the only incentives that participants thought could motivate non-academics to conduct research. Non-monetary incentives suggested were similar to those described in the previous case studies: valuing research experience in career progression, offering leadership positions on trials, attendance at international conferences, and authorship on publications. The need for a more meritocratic approach to medical career progression based on research was explained by the director of the international research network:

“We need career development and a clear promotional structure and job positions based on CVs and professional development points, so when you apply for a job it [research] is taken into account and jobs are based on this experience. Currently once you have a medical degree and a post, only your time of service is taken into account and your clinical progression, nothing else matters so there are no incentives to take on any other

responsibilities for extra points. At universities this is different though, and research and other work are given credit for career progression.”INT.14.PPT.1

However, even among academics, local collaboration was rare. This was seen to hinder the quantity and quality of research conducted in Sri Lanka, as explained by this academic:

“We have identified important research questions that need to be addressed. But the main problem is actually, there is not sort of a collaborative platform to discuss this among the clinicians, because many people are not willing to collaborate. People do research in an isolated way, rather than working as groups... So when that happens they can’t attract too many people because the funding is low and then they can’t come up with good quality research. So what we need, my second point, we have to have good productive research collaborating networks.” INT17.PPT.1

This was reportedly due to hierarchical and competitive recognition structures encouraging academics to be individualistic. Therefore it is questionable whether improving incentives for clinicians would encourage collaboration between professional groups. Although this situation is similar to that described in the Cameroon study, it is important to note that in Sri Lanka these relational issues did affect support of junior staff. Indeed, junior researchers reported excellent support from both academic and clinical staff. A PhD student explained his experience of this by saying:

“Yes, I got help from MOIC, Medical Officer In Charge and the young medical doctors in the region, they helped me a lot. They allowed me to use their laboratories. Then there are doctors who are working at the peripheral hospitals and other paramedics, nurses, and technical staff, they are usually very helpful. Those are the people who helped me in the last ten to twelve months... The other thing is, you know, many doctors who are working in the region are our class mates or our supervisors so they usually extend the maximum help to us. In fact, the medical crowd in this country, they are like a family. Whatever their research, or activity performed in the different parts of the country, they think this is their responsibility to help.” PM.7.PPT.1 PhD researcher and clinician

Although this respondent was a clinical academic, and therefore may have got special treatment because he was one of the medical “family”, he said that he would expect this support to be extended to any students, even international ones³.

6.3.4.6 *Material resource availability*

There was relatively little discussion on material resources and participants did not say they had to invest a lot in research sites to be able to undertake trials. Therefore material resources appeared to be less problematic in Sri Lanka than in Ethiopia and Cameroon. The exception to this was laboratory setup and resourcing. Technologically advanced equipment was lacking in many institutions and even simple machinery such as minus 80 degree freezers were unavailable in healthcare institutions and less established universities. The only examples where laboratory issues were not reported as problematic were studies that only required simple analytical tools and in the international research network facilities because advanced laboratories were available.

Like in Ethiopia and Cameroon, this could reportedly result in certain research being dependent on foreign collaborators to analyse samples. This was problematic because it meant that local capacity to analyse samples was never developed, as an academic clinician working in a less established university explained:

“Most of the time researchers need to find a foreign collaborator with the lab facilities. But what they are doing is providing material for a foreign collaborator to use outside – they are not doing the research here. In [doing] that you and your laboratory staff will not get trained... They never learn how to do it and the skills are not developed.” INT17.PPT.1

³ From personal experience of conducting this DPhil in Sri Lanka, this supposition was true; both academics and clinicians went out of their way to help my research.

Also similar to the previous case-studies, access to literature was variably problematic due to intermittent availability of HINARI. Where participants had full access they felt it provided most of the literature they required. However many participants said they had limited or no access to HINARI and without this literature availability was limited to open access journals and abstracts. Unlike in Ethiopia and Cameroon, internet access was not reported as problematic.

6.3.5 Trial operations and management

Barriers to trial research impacted on trial operations in remarkably similar ways to those described in Ethiopia and Cameroon. The operational issues and their causes reported by Sri Lankan participants are shown in table 6.3. Like in previous case-studies, difficulty with publication and research dissemination were frequently encountered problems in Sri Lanka and one participant argued that they should be considered an important part of trial operations. Therefore publication and research dissemination have been added to this table.

Table 6-3 Operational issues and their causes reported by participants in Sri Lanka

Operational stage	Operational experiences reported by participants	Drivers of operational experiences reported by participants
Thinking of research ideas	• No difficulty	• There are plenty of research topics that need to be addressed
Writing proposals	• Several participants reported difficulty writing research proposals or having reviewed poor quality proposals	• Lack of exposure to research & experience in writing proposals • Limited training availability • Limited time to write proposals
Securing funding & sponsorship	• Local funding was generally available but only for smaller grants. This resulted in financial constraints. • Many participants had difficulty competing for international funding	• Sub-standard protocols • Limited research track record or credibility to compete internationally • Poor grant management capacity & research support • Limited research investment
Designing study & writing protocol	• Hard work but no major problems	• Support from colleagues & advice in international guidelines from groups like the WHO were helpful
Securing ethics & regulatory approvals & admin permissions	• Ethics approvals were normally not problematic but some participants reported approvals taking up to a year. • Regulatory approvals could often be slow. This was worse for novel interventions • Admin permissions could be problematic depending on the number required & the supervisor's attitude to research	• Some inexperience in reviewing clinical trials & lack of staff & resources to review applications • Limited regulatory capacity • Bureaucracy meant several approvals were required & some supervisors were suspicious of research & held up permissions
Completing administration tasks	• Administrative procedures such as purchasing & fund management were very time consuming & slow • Administrative rules frequently hampered research operations	• Bureaucratic procedures • Little administrative research support • Outdated financial regulations
Completing logistical tasks	• Logistical tasks for clinic based work was not problematic, but field based research was difficult if resources were scarce e.g. availability of suitable freezers & transport	• Limited funds to meet logistical needs or inability to use funds due to outdated financial regulations • Poor transport & communication links in rural areas

Recruiting, managing & training staff	• Clinical trials were frequently short staffed, especially if locally-led • Skilled staff were normally available but difficult to recruit and turnover was high • Few cooperative clinicians available • Training was rarely problematic	• Financial restrictions means money for additional staff is not available • Financial regulations may prevent support staff from being hired or enforce uncompetitive salary rates making it hard to recruit staff • Research culture divide between academics & clinicians
Setting up & running a laboratory	• Skilled laboratory staff in short supply • Laboratory resources were sometimes lacking, especially in more advanced equipment -Samples may have to be sent abroad for analysis but storing & shipping was difficult • University labs were generally better resourced than clinic labs	• Laboratory capacity was mostly limited by financial constraints • Low wages made it difficult to hire & retain lab staff • More established research groups had accumulated equipment through successive grants but new groups had limited facilities • Research has a low priority in clinical environments
Recruiting & managing patients	• Patients usually readily available and willing to participate • Careful patient management is required in rural communities • Recruitment in clinics difficult when clinicians uncooperative	• Large patient pools & patient culture is usually to oblige clinicians • Rural patients generally have little understanding of research • Clinicians often dislike standard practice guidelines & research • Few incentives for clinicians to participate in research
Data management & monitoring	• Data management & statistics skills in very short supply • Cases of bad data management due to untrained individuals • Mistakes made in power calculations, randomisation & analysis	• Insufficient statistics training available • Lack of money to hire a dedicated data management staff • Difficulty accessing or paying for software
Publication & research dissemination	• Research dissemination was a neglected area of research • Several reports of research being conducted but not published • Dissemination through conferences was popular and easier than publishing in journals, but funds for travel were restricted • Flaws in study design prevent publishing in journals	• Skills in writing for academic journals were lacking & little publication support was available • Few scholarships for international conferences are available • Making time for publication or applying for scholarships was difficult • Lack of expertise in trial design and statistics

Like in the previous case-studies, most participants found the start-up stage of trial conduct most challenging. They reported that if the study had been planned well, then following on from patient recruitment was usually relatively trouble-free. However, other participants felt this was dependent on the specific trial, and continuing trial management could be very demanding, especially if there were few study staff or limited resources. Hiring staff for project-specific research grants was particularly problematic because skilled researchers were reluctant to take low-paid short-term contracts. However, even when higher salaries were offered staff turnover was high. The international research network had reportedly overcome this problem by maintaining detailed professional development records for trial staff. This way staff felt motivated by professional development and they could be tracked and re-recruited if new funding became available.

Operational experiences also differed by where the trial was conducted. University-based studies were reported as being easiest because they had dedicated space and resources for research. However their distance from patients made recruitment more problematic. Community studies all reported easy recruitment but that resources for analysis were scarce and logistics were made difficult by the rural conditions. They also found that managing patients was more complicated and time consuming because rural communities often had more ongoing concerns about research. For instance, they may regularly call the trial PI to check if they were allowed to eat certain foods or go to funeral services while being enrolled in the trial. This was reportedly due to them having less understanding of research and experience with medical care. Clinic or hospital-based studies were frequently reported as most difficult because research was often not welcome in these settings. The reason for this attitude was the aforementioned

lack of research culture in clinical environments. This made gaining administrative permissions, support of healthcare staff, referrals for recruitment, and allocation of resources very difficult. According to several reports, prevention of recruitment by uncooperative clinicians was one of the most rate-limiting steps in trial conduct. Conversely, if clinical staff were supportive of the study, they could be extremely helpful by facilitating recruitment and other operations. One approach used by an investigator to facilitate medical staff involvement was to provide additional healthcare staff to relieve the extra work pressure caused by the clinical trial.

Overall there was no single major issue or silver bullet to improve trial operations, despite the fact that some respondents felt that money was at the heart of most problems and solutions. Instead, like in Ethiopia and Cameroon, most respondents said that the key to successful trial conduct was good planning based on experience, attention to staff management and the forging of strong relationships with stakeholders. In this way, most operational issues could usually be avoided or overcome.

6.3.6 Developing organisational synergies

Several participants reported that leveraging local organisation synergies was a particularly powerful enabler to trial conduct. This was because although human, material and financial resources were present within the research system, they were often isolated and thinly spread, which made forming a critical mass to perform more ambitious projects difficult. By combining resources between stakeholder organisations, a critical mass could more easily be reached. Pooling human resources to form larger research teams was particularly enabling, as this academic clinician explained:

“So if you have a good statistician on board and if you have a pharmaceutical person who can give you direction – you know, I think you must have a team. A team is absolutely essential. There is no doubt about it. Everybody has to be committed. Everybody has to do their part. If you have a good team and little bit of extra funding so you can afford a research assistant, you can learn and it [clinical trial] is not difficult to get through.”

FGD.8.PPT.1

Sharing staff between academic institutions and government departments was also reportedly a good way to involve local stakeholders who had intimate knowledge of the context and who could act as gatekeepers. Furthermore, since most workers were already employed by the government, they often did this extra work on a voluntary basis. In addition to human resources, government departments also contributed material resources such as laboratory facilities, transport and accommodation. A PI of a school-based clinical trial explained the importance of her relationship with the local branch of the ministry of education and health:

“We involved the Education Ministry staff. Because we were working with them they helped us to find the teachers who could do the assessment for us and to find the research assistants. We didn’t even need to advertise, it was all by word of mouth...The teachers in the schools were even the ones giving treatment. We met with all the teachers and gave them instructions, trained them in drug dispensation and how to handle adverse events and record on data sheets, all of that... We also couldn’t have done it without the hospitals involvement. In some of the districts we used university parasitology labs, but in other places we used hospital labs. And then arranging the transport was also a big issue as there was a lot of travelling to do, but again it was networking and using our contacts with the Ministry of Education officials to get local people to hire us vehicles.” **PM.4.PPT.4**

The benefits of good relationships were not just limited to traditional research actors and direct stakeholders. Participants reported that good relationships with funders, banks and pharmaceutical companies had smoothed operations and opened up a multitude of research opportunities.

These reports on the importance of teamwork and collaboration are similar to opinions expressed in Ethiopia and Cameroon. Furthermore, strategies to facilitate

their formation were similar to those described in Cameroon when creating stakeholder buy-in. However, some Sri Lankan participants appeared more successful at forming inclusive research teams, despite the aforementioned professional relationship issues, and offered greater details on how they could be developed. The reported key to overcoming professional divisions was building up trusting relationships through regular contact. Some experiences of the importance of this are shown in box 6.4

Box 6-4 Participant explanations of the importance of maintaining good relationships with clinical staff and management

*“Working as a team and having good relationships is important, especially with doctors and nurses to make sure they are happy and will cooperate. If there is bad management or the hospital management is not on your side, the junior doctors will not help, so you need all levels of support and cooperation.”***INT.14.PPT.1 Director of trials unit**

*“I did community medicine and I know how difficult it is to get the approval from the regional district provincial directors. So, my first task would be to get to know the regional person and the national – otherwise you will never get it off the ground.”***FGD.5.PPT.2**

*“I think there is a very healthy relationship – we have very good connections with the ward staff and that is very helpful. I don’t think any other organisation can get the same relationship. Like, if a newcomer comes to the ward, I don’t think everyone will be such help, but for us we have a special, healthy relationship with ward staff and hospitals.”***FGD.12.PPT.3 Clinical trial project manager**

To achieve this, respondents said stakeholders needed to be convinced of the value of research and its outcomes. Emphasising patient benefits, use of future therapeutics for medical staff, and describing research as a service to society were reported to be convincing ways of getting stakeholders buy-in. One senior academic explained that he held regular information sessions to do this, and during these discussions it was essential to demonstrate your competence and explain patients

will be getting the best possible treatment. This was deemed so important, procedural and political that one public health practitioner who had conducted locally-led trials described the process as “canvassing”:

“Actually, I wouldn’t really describe it as permission. You have to canvas them and then they will give you permission. Some will give you permission, but you have to talk to them. In X district it’s okay because we have MSc and MD qualified people in charge so they know what is happening. But in other places it’s very, very difficult to make them understand...You need to inform them early on and then engage them in the clinical trial. Because they are not used to it, so if there is a national body on clinical trials, we need to get the provincial people involved in that. ”. FGD.5.PPT.1

Another trial group that had a good track record of influencing policy had a dedicated liaison to maintain political links. She explained the need to ensure early and ongoing engagement with policy actors and to include them in any side-benefits arising from the research, such as capacity development, short-term employment, authorship on publications and opportunities to present research findings. However one participant suggested that this sort of engagement took too much effort for most researchers to be able to commit to and instead suggested the use of an intermediary group who could collect and evaluate evidence and present this to policy makers on behalf of researchers.

6.3.7 Individual enabling characteristics

Personal characteristics and attitudes reported to enable trial leadership in Sri Lanka were very similar to those suggested by participants in the Cameroonian case-study. These included: being positive, persistent and tenacious in the face of limited resources and challenging environments, having a flexible and creative approach to overcoming problems, having strong interpersonal and negotiating skills, being able to successfully “canvas” stakeholders and collaborations, and being a good manager who could form and maintain effective teams.

Although lack of self-efficacy was less reported in the Sri Lankan case-study compared to the Ethiopian and Cameroonian studies, several participants did say that self-belief and confidence in your own abilities was very important for helping to display the aforementioned enabling characteristics and attitudes. Furthermore, as also found in the Cameroon case study, Sri Lankan respondents said that belief in their own work abilities was developed through work experience in positions of responsibility and expert knowledge of clinical trials. However some trial inexperienced researchers said they became more self-confident as a result of having good mentorship and expert support. Box 6.5 shows example quotations on the importance of enabling personality characteristics and how these were developed.

Box 6-5 Example quotes on the importance of positivity, tenacity and self-efficacy

"I knew I was doing the right thing and there were no ethical issues involved and that they [the ethics committee] were just being bureaucratic and over-cautious, and so I just kept on going. I wanted their reasons for not giving approval, and then I justified all that... I had to write several letters asking them to send to external reviewers and others who have expertise, to get them to comment on the trial and give their opinions. So I think that if you know what you are doing is right, and you can prove it scientifically, although you might have problems, you can probably get things done." **INT.11.PPT.1 Clinical Trial PI**

"Since I like doing research, I like to write proposals. Some get rejected but I always keep trying." **FGD.8.PPT.2 Academic**

"I think I'm quite confident in doing them [clinical trials] , because I have gone through this and I know how to do it and in fact, once this is over, though it is hard work, I still catch myself thinking what would be the next steps." **FGD.8.PPT.1 Academic clinician and trial experienced PI**

"I have never been involved in any other trials but he has [refers to trial experienced senior colleague PM.4.PPT.2], and I think that was what gave us the strength to strike out on our own and figure out yes, we could do this! I'm basically a parasitologist, I'm a lab person, but the professors' input on the trial really helped". **PM.4.PPT.1 Head of academic department discussing his first clinical trial**

6.3.8 Promoting a research culture through exposure and awareness

Several respondents thought that the number of locally-led clinical trials could be increased by fostering pro-research research cultures in healthcare institutions, and this could be achieved through increasing exposure to trials. They suggested that this would make doctors more aware of trials, increase the value of research, and encourage more doctors to work with academia alongside their clinical practice. They also felt that because suspicion of trials was rooted in lack of understanding, exposing healthcare decision-makers to the method and its benefits would reduce deliberate delays in research permissions.

This exposure to clinical trials, and research in general, could reportedly take several forms; modules in undergraduate curricula, continuing training in research methods, undertaking clinical trials for PhDs and MD qualifications, workshops, and experience exchange opportunities. However, the critical element of the various modalities was that they should make stakeholders value clinical trials. Box 6.6 shows illustrative quotes on this issue.

Box 6-6 Participant opinions on the need for research exposure and awareness of clinical in healthcare contexts

*“The clinicians are not used to trials and are concerned about them and suspicious. It makes them uncomfortable because they do not have experience in this area. You see, it is rare for junior doctors to come across clinical trials. They need exposure to trials and it to be built into their curriculum.”***INT.14.PPT.1 Consultant doctor and director of a research unit**

*“People need to be made aware of these trials. I think there has to be more explanation of the concept of clinical trials in Sri Lanka. It’s not in our normal day-to-day priorities you know, it’s not in our work ethic, the value of clinical trials and the application of findings locally. This attitudinal change can be brought about by increased awareness, having open forums and incentives... We have to show the outcome of these trials. That will show that they are important. Then people might end up doing some!”***FGD.8.PPT.1 Academic clinician and trial PI**

*“I feel that trials, research, the two words are not well understood by the medical community, at least in the Ministry Of Health. Once the research students leave the faculty, they are viewed with suspicion. The doctors and other healthcare professionals should be made more aware. Giving an idea about what is research, why it is important, research methods and even a basic understanding of data analysis would help.”***FGD.5.PPT.3 Associate professor and trial PI**

6.3.9 International Collaboration

Foreign collaborations were reportedly more common than local collaborations in Sri Lanka. This was partly due to academic competitiveness and relational issues making local collaboration difficult, but foreign collaborations were also favoured because they commanded resources that were not available locally. This situation was very similar to that described in Ethiopia and Cameroon and the benefits of foreign collaborations reported by Sri Lankans were also the same as those listed in the previous case-studies. A quotation by a community based public health practitioner describing her experience of foreign collaboration demonstrates the importance of foreign resources for facilitating trial operations:

*“I got the fullest support from the foreign collaborators. So when I needed a vehicle, I didn’t have to look for it, there was no issue because it was funded. I also didn’t have to worry about other things. I got three people, I trained them, and I could arrange accommodation for them. We could provide the benefits the staff deserved at the real current rate; the doctors needed to come to their private practice or their locum for this research but without those benefits, they wouldn’t come. Normally there are limiting government regulations, but with the foreign collaborators I didn’t have this problem... I had a busy schedule, so I could hire someone else to cover some of my routine duties. They gave me the money to hire a data entry person and it was done. Now everything is finished. So it was all very smooth and streamlined. They provided all the support I needed; otherwise I couldn’t have done it.” **FGD.5.PPT.1***

As also reported by Cameroonian participants, some Sri Lankan respondents also strongly valued the less hierarchical culture typically fostered in foreign-influenced research. These flatter organisational structures were felt to encourage teamwork by making everyone feel more valued and building closer relationships through better communication and mutual understanding. This reportedly improved motivation within teams which encouraged them to take on more complex duties and reduced staff turnover because they were more content in their jobs. It also helped colleagues to support each other because they shared common goals and understood colleagues’ needs and wanted to help each other out. One example of this was taking on other colleague’s duties when they were overburdened, as explained by these trial colleagues who worked for the international research network:

PPT.3: *“The team, the excellent team. I think one of the best teams in the whole world! We had the most friendliest and supportive team at the initial stage, including the programme director. So it was, like, very motivating. Even though it was a very difficult task to accomplish the organisational goal, it was challenging, but still we enjoyed the life a lot. It was one of my best periods in my life! We had the opportunity to talk to each other and encourage each other. So that was very supportive to everyone and we even personally helped each other...It was wonderful”.*

PPT.4: *“In Sri Lanka, they have a hierarchy system. You will see many companies build a hierarchy system. I came here and fortunately we got guidance from our foreign*

proposers, so they were trying to remove all the layers, remove the hierarchy, they are trying to manage a flat structure... It's important because it's team-building"

PPT.3: *"Basically, running the trial was everyone's target and I didn't limit my role and we didn't even have a job description or anything. We had to work on everything as a mass, I mean, we all had a similar experience. So someone didn't even need to ask to delegate work. So the [clinical trial] was the final target of everything, and even though there were limited resources, it [the teamwork] was encouraging. There were no, like, hard feelings or anything. FGD.12*

As also reported in Cameroon, collaboration with foreign groups was also valued for the credibility it would add to projects. Several Sri Lankan respondents felt that their grant applications, regulatory clearances and publications were more likely to be successful if they had a prominent foreign name on the application form, regardless of whether the foreign group had actually made improvements. The head of an academic department explained her experiences of this:

"You can do it on your own, but I have found that publishing the research and also the acceptance and the credibility, and also I think the ethics committee's will be more happy with studies that have more outside members. Because I think that puts the credibility and validity, which should not actually be the case, as far as I think." FGD8.PPT2

However, some Sri Lankan respondents had similar concerns about international collaboration as those described in Ethiopia and Cameroon. Participants who had experience of commercial and non-commercial foreign collaborations said the key to avoiding these issues and creating good partnerships was strong local inclusion and leadership and ensuring sharing of benefits through capacity development. A medical association chair explained his policy on international collaboration:

"We should take something away from this [collaborative trials] in the way of transfer of knowledge and equipment, and wherever possible, let's do the investigation in this country, rather than just sending samples away. So we explored that aspect of getting benefit for the country and for the population." INT.2.PPT.1

The international research network described in section 6.3.2 (page 236) was frequently regarded as an excellent model of research partnership. This was because it: had a mix of foreign and local leadership, was highly inclusive and aimed to develop local capacity, focused on locally relevant issues, all research was conducted in Sri Lanka, organisationally it had flat management structures and reportedly excellent team working, and great effort was put into local networking, embedding in local institutions and influencing policy. As such they were one of the most productive research groups in terms of clinical trial output in Sri Lanka.

6.4 Discussion

This chapter aimed to identify, understand and explain the barriers and enablers to trial conduct in Sri Lanka, particularly how locally-led trials are facilitated, and consider which components of the theoretical framework have wider generalisability.

The results represent a detailed account of the Sri Lankan research system, and explore in-depth how the various local system components sometimes supported locally-led trial conduct, but can also be counterproductive and divisive. Experiences with trial research were quite diverse, which reflected the differential presence of barriers and enablers for different research institutions and professions. While this was also true in Ethiopia and Cameroon, variable success in trial conduct in these countries was mostly influenced by the extent of foreign support and trial type, with the local research system appearing to provide little support for trial conduct.

Interestingly, most of the barriers and enablers to trial conduct in Sri Lanka were very similar to those experienced in Cameroon and Ethiopia. Indeed all

barriers identified in the theoretical framework were present to some degree and there were no distinct new enablers that explained the greater conduct of locally-led trials in Sri Lanka. Rather, it appeared that locally-led trials were facilitated by incremental reductions in previously identified barriers and stronger and greater provision of enablers. As such, Sri Lanka seemed further along a continuum towards an enabled research environment, which although not perfect, supported more locally-led trials than the less developed research systems of Ethiopia and Cameroon. Therefore, while the degree of the barriers and enablers to locally-led trial conduct vary by profession, institution, trial type and location, it appears that the theoretical framework captures most of the issues determining locally-led trial conduct in fairly diverse research contexts.

The following discussion will more specifically explore how locally-led trials were enabled and prevented, consider where the Sri Lankan findings strengthen and provide greater detail to the theoretical framework, and how new opinions and experiences can be accommodated.

6.4.1 The research system

Stewardship of clinical research in Sri Lanka was interestingly capricious. Despite a number of local funding bodies and greater grant availability compared to Ethiopia and Cameroon, research was still relatively underfunded due to the limited value of local grants. This appeared to reflect fiscal constraints and mixed attitudes to research by senior decision-makers. Unusually the top-level drive for clinical trials and health research came from financial ministry departments that valued economic and capacity development benefits, rather than potential to improve health outcomes. As such foreign commercial studies were actively encouraged.

Conversely, the ministry of health generally took little interest in research or evidence-based medicine.

Although this conflicts with some traditional views on the purpose of trials and who should value research, it nonetheless enabled the conduct of less resource-intensive locally-led trials and led to improvements in health-policy. Foreign-led trials including commercial studies also provided important early trial experiences, raised technical capacity, provided exposure to new techniques and ways of thinking, led to some material improvements and injected foreign capital. Therefore the Sri Lankan case-study provides valuable evidence of the benefits of modest investments and the need to advocate to a variety of stakeholders with specifically tailored arguments, especially if traditional stakeholders are proving unreceptive. Consideration of this is likely to be important for many LAMICs because in Ethiopia and Cameroon advocacy was needed to increase national investment in research, and in all three case-studies health research was not strongly valued in healthcare systems.

From a governance perspective, the Sri Lankan case-study also shows the importance of having decision-makers who understand research and value it as a means to economic and health development. Where decision-makers had a negative attitude towards research and evidence-based medicine, this could hinder investment, research permissions, access to patients, research uptake, and generally result in a disabling research culture. However, where leaders were committed to research, they greatly enabled processes by providing encouragement, support, taking an interest in research findings, and fostering a research culture. In all case-studies research cultures were weakest in healthcare institutions and strongest in universities and academic departments.

The strong culture of research in academia in Sri Lanka provides a good example of how requiring academics to conduct research and linking this to career progression can make research more of a priority and commonplace. Although human and material resources were reportedly far from ideal, the modest investments made and clear institutional buy-in for research nevertheless fostered a more vibrant research environment. This strongly supports arguments made in Cameroon and Sri Lanka that research must be central to career progression and appreciated by decision-makers if a culture of research within everyday practice is to be developed. However, while this dedication to academic research in Sri Lanka resulted in positive research outcomes in universities, healthcare institutions still largely lacked pro-research cultures due to limited top-level appreciation and buy-in for research. This was also true for Ethiopia and Cameroon.

Professional segregation and differences in research rewards and incentives for clinicians and academics appeared to exacerbate professional tensions in Ethiopia and Sri Lanka, and in all case-studies this isolated healthcare workers from research. This situation is highly problematic because healthcare workers have the potential to be a huge asset to the research system. Furthermore, although Sri Lanka had strong academic research cultures, local collaboration among academics was similarly problematic in Sri Lanka as in the other case-studies. This seemed most severe in Cameroon, possibly due to contributory cultural factors. However, in all cases this was attributed to individualistic and competitive attitudes, which also appeared to be due to the structuring of incentives. Since recognition was dependent on gaining grants and authorship on papers, and these were made inherently competitive by research award systems, then local researchers became competitive towards each other and were reluctant to collaborate with peers

because they were competitors. Although this applies to academia globally, it is understandable why competition and jealousy are intense in resource-limited settings because there are much fewer rewards and research opportunities to compete for. These suppositions are strongly supported by theories on organisational team working that show making rewards contingent on individual performance and competition significantly reduce helping behaviours, collaboration and teamwork [266]. This would also explain why academics willingly collaborated with foreign researchers and sometimes supported students because these actors would generally be competing for different resources and on separate rankings.

From a regulatory perspective, ethics and regulatory boards were functional in Sri Lanka. However they still suffered similar capacity constraints as those described in Ethiopia and Cameroon and in all countries this impacted on trial operations in similar ways. It also meant that there was no spare capacity In Sri Lanka to accommodate the expected increase in demand from commercial studies. Although this was due to be addressed in an upcoming clinical trial act, reported low priority in government departments meant that these acknowledged deficiencies were still unresolved (as of 25/06/14) despite several years of attempts. This once again shows the importance of harmonising research strategies and buy-in for research because although some actors were working hard to improve regulatory capacity, other stakeholders were hindering the process.

Slow procedures and administrative delays were also caused by overly centralised, hierarchical and bureaucratic organisational structuring. These were present and deemed highly problematic in all case-studies. Participants in both Cameroon and Sri Lanka made similar suggestions to improve and streamline procedures. However, in both cases, rules and procedures were reportedly resistant

to change and thus remained outdated and unfit for purpose. These findings agree with a Swedish International Development Agency review of challenges when shaping capabilities for research in Sri Lanka that identified the following factors as having contributed to low research productivity in the universities environment: “insufficient support funds, difficulties in procurement of research equipment and consumables, high degree of bureaucracy and procedures to purchase consumables and equipment, weaknesses in supply chain and excessive reporting and evaluating procedures” [12]. Based on the literature presented in the chapter 5 discussion, inefficient and bureaucratic administration systems appear to be commonly problematic in many LAMICs, not just in health and research sectors, but throughout public administration. Therefore any meaningful improvement is likely to require more widespread public sector reforms that are outside the scope of most research actors to address.

Fortunately, although these structural issues were problematic in Sri Lanka, trials were still being conducted in increasing numbers. Therefore although these structural issues caused difficulties, they did not appear to be critical impediments to research. Furthermore, unlike in Ethiopia and Cameroon where the main solution to these problems was bypassing local systems which resulted in them failing to develop, Sri Lankan investigators appeared to manage within local systems. The trick to this appeared to be building quality working relationships and stakeholder support through close engagement. This provides support for similar arguments made in Cameroon. Further details on how this was achieved in Sri Lanka are presented in section 6.4.3 (page 289).

Based on the limited discussion and complaints about material resources, it appeared that they were less limiting than in Ethiopia and Cameroon. Indeed, within

academia, material resources were largely adequate to allow a range of self-sufficient research. However, lack of more advanced laboratory equipment could restrict the scope of studies because local investigators found it very difficult to obtain larger international grants to buy these more expensive resources. Like in Ethiopia and Cameroon, success in gaining international grants appeared mostly dependent on foreign collaboration and support.

Although the Sri Lankan research system had similar skills gaps to those observed in the Ethiopian and Cameroonian case-studies, on the whole Sri Lanka appeared to have greater availability of trial expertise. While it is not possible to quantify this because all reports were based on relative opinions, the greater propensity for locally-led trial undertaking provides evidence for this. Examination of the differential reports of barriers and enablers to provision of human resources for research allow some explanation of why this was the case.

All case studies reported very similar issues with the development of human resources for research, stating that there was insufficient attention to research in training and education. Although this was more severe in healthcare contexts, in all case studies this situation was also deemed to be problematic across the board. These findings are also congruent with the findings of a Sri Lankan author who argued that the Sri Lanka medical system lacked a research culture and education was too theoretical and lacked research components (Waidyanatha 2002 in [130]). Therefore it seems that didactic training availability cannot account for the wider availability of trial staff and leaders in Sri Lanka. Furthermore, participants in healthcare institutions in Sri Lanka reported similar, although less severe barriers to the effective use of human resources for research as those described in Cameroonian and Ethiopian academic and healthcare contexts. These included:

limited awareness of trials and low motivation and self-efficacy to conduct them due to poor research cultures, little exposure to trial conduct, lack of time and few incentives for conducting research.

Therefore the greater availability of human resources for research supporting locally-led trial undertaking in Sri Lanka appeared largely driven by academics. Participant reports also confirm this. This appeared to be due to fewer problems with awareness of trials and research, and greater motivation and self-efficacy to conduct them. Indeed, no academics cited these issues as particularly problematic. Participant reports make it clear that this was because academic departments had strong research cultures, incentives and accountability to conduct research, strong junior-level support and mentorship. It is also likely that greater conduct of locally-led trials in academic institutions meant that there were sufficient opportunities to be involved in research and clinical trials. Although not specifically stated as such, this is supported by no academic participants considering opportunities to work on trials as a barrier to their professional development. Accountability to conduct research for career progression appeared particularly important because some academics said that they would not have conducted research and trials if this was not required of them.

Although academics did not cite self-efficacy as a barrier to trial conduct, they did report having self-efficacy as being very important for enabling leadership of trials. This was because it not only gave them self-belief that they could lead trials, but also supported enabling individual characteristics and behaviours that helped them to run trials. Like in Cameroon these leadership behaviours included: being positive, persistent and tenacious in the face of limited resources and challenging environments, having a flexible and creative approach to overcoming problems, and

strong interpersonal skills. Furthermore, the development of this self-efficacy was reportedly promoted by trial experiences that gave responsibility and inclusion in management aspects, but also having support from mentors with expertise in clinical trials. This strongly supports arguments from Cameroonian participants and the literature presented in the chapter 5 discussion on the importance of self-efficacy for trial leadership behaviours and also how self-efficacy and leadership is developed.

Sri Lankan and Cameroonian reports also agreed that, in comparison to foreign-led trials, working on locally-led trials was not only more motivating but also better developed self-efficacy and leadership. This was because they offered more opportunities for responsibility and independently overcoming challenges. This particularly applied to more senior researchers who were at a stage in their career where they wanted to develop these professional aspects. Therefore it appears likely that the greater propensity for trial undertaking in Sri Lanka was also driven by the greater opportunities to be involved in locally-led trials in Sri Lanka compared to Ethiopia and Cameroon.

6.4.2 The need for applied locally-led clinical trials

Although Sri Lanka was more productive in terms of locally-led trial conduct than Ethiopia or Cameroon, this was still regarded as insufficient by all Sri Lankan respondents. Like in the previous case-studies, most Sri Lankan participants stated that more local trials were needed to address persistent local evidence gaps. While this was in part due to the current number of trials being insufficient to meet research needs, it also appeared that part of the problem was that much of the current research was not useful for policy.

This was reportedly largely due to the fact that the majority of research was an academic affair. This is confirmed by a review of Sri Lankan published health research which shows that academia accounted for the vast majority of publications and hospitals only contributed 16.4% of total national research output [261]. Participants consistently reported that research and even trials were done more for academic progression rather than impact, and supply-led funding strategies allowed investigators to follow their research topic of choice. The limited value of research grants and restricted material capacity also reduced the scope of research that could be attempted, and failure to collaborate locally prevented pooling of resources to reach a critical mass that would enable larger, potentially more useful projects. Structural and professional exclusion of healthcare institutions and ministry departments in research also meant that research may not be correctly targeted or practical enough to be of use for policy. This findings agree with the previously mentioned Sri Lankan author who termed Sri Lankan research outputs as fragmented [130]. Furthermore, many participants said they lacked skills and time to write up research, so results often went unpublished. This not only meant that research often failed to improve healthcare outcomes, but also reinforced negative perceptions that local research and evidence was of little use. Far from being restricted to Sri Lanka, these issues were also prominent in the Ethiopian and Cameroonian case studies. Indeed, recognising that much research in LAMICs is isolated and academic, the 2013 World Health Report specifically recommends that health research should be embedded in healthcare institutions and include all stakeholders to have a realistic chance of policy impact [1].

6.4.3 Facilitating collaboration and teamwork

Encouraging trial conduct outside of academia and facilitating more inclusive local research collaborations could not only increase trial conduct, but also the impact of research. Reports from Sri Lanka and Cameroon also suggest that the quality of team work in collaborations was important because it could improve the efficiency and productivity of research by increasing staff motivation and the taking on of higher roles and responsibilities, encouraging peer support and knowledge sharing, sharing of work burdens, and reducing staff turnover. As suggested in the chapter 5 discussion (section 5.5.3 page 226), the more open and sharing environments that team working fostered should also help develop communities of practice which would support learning from colleagues, and indeed this was reported in both Cameroon and Sri Lanka.

Regarding forming more inclusive research collaborations, many respondents from all case-studies felt that increasing exposure to trials would help breakdown negative attitudes and inculcate pro-research cultures that would make collaboration more possible. However, participants belonging to research groups in Cameroon and Sri Lanka that successfully forged inclusive collaborations provided clearer details on how this could be achieved. Rather than passively attempting to build stakeholder buy-in, their techniques were much more active, personal, and strategically targeted at individual stakeholders. This reportedly enabled them to present the most convincing arguments to different stakeholders at the correct time, and build up personal connections and trusting relationships which broke down professional divisions. Their techniques included regular and early engagement, establishing oneself as an informed and reliable authority, and demonstrating the

benefits of the research for both patients and the stakeholders themselves, and being persistent in the face of resistance. As such, two participants described this behaviour as “diplomacy” or “canvassing”.

That these techniques are effective at forging quality relationships and influencing stakeholders is supported by theories of “issue selling”. This is because the strategies described by participants closely match behaviours identified as helpful to “issue selling” [267]. Issue selling is a management concept describing the process by which individuals affect others’ attention and understandings of events with implications for an organisation’s performance [268]. As such, organisational change is not a discrete event affected by only senior decision makers. Instead, mid-level actors can also be potent initiators of change by using distinct strategies to affect top management attention in favour of their “issues” [269]. Issue selling is therefore important for organisational performance because it focuses attention on a rich source of bottom-up ideas and is thought to be a key skill that managers should have [267]. However, despite the apparent effectiveness of this technique for improving research operations and outcomes, it was clear from participant reports that this took a great deal of time and effort, which one Sri Lankan participant thought would be too much for many investigators to be able to commit to.

Although it was unclear how participants learnt their “issue selling skills”, Sri Lankan and Cameroonian reports of good team working suggest that issue selling is supported within environments where there is trust, communication, mutual understanding, receptive and supportive leadership, and a collaboratory attitude open to “bottom up” initiatives. This is important because these team environments make staff feel valued and confident enough to be comfortable sharing ideas and

canvassing stakeholders. Therefore good team working is not only important for research productivity and learning, but also development of issue selling skills. Although this information was inferred rather than explicitly stated, it closely matches theoretical drivers of issue selling behaviours [270], and therefore appears plausible.

Regarding the development of effective team dynamics, the critical component mentioned in both Sri Lanka and Cameroon was having management that provided at least some of these factors: including staff in professional development activities, making everyone feel valued through recognition, providing opportunities for diverse, rewarding and challenging work, giving responsibility and freedom, and offering support and encouragement. These arguments on the benefits of team working and how it is developed appear highly plausible because they closely match theories on the effects and development of teams [271-273]. Additionally, participants from both Cameroon and Sri Lanka said that less hierarchical structures were more conducive to creating teams with these attributes. This agrees with research in labour productivity which found that flatter hierarchies are conducive to teamwork and employee cohesion, and these in turn lead to improved organisational productivity [274]. These flatter management structures were more typically associated with foreign-influenced organisations. However, some local investigators also reportedly displayed these management styles.

Once again, while it was not exactly clear how good team leadership skills were developed (this is a recognised problem in the literature [275]) junior staff clearly stated that their team working skills were improved by working on research projects that allowed them responsibility, particularly those that had good team dynamics. This is supported by theories of teamwork that suggest staff adopt the management

styles that they have been exposed to, and gradually become leaders as they receive more responsibility [275]. Furthermore, this supposition appears to tally with the previous work experiences of reportedly good team managers, because most of them had extensive experiences of working with international partnerships which were widely regarded as having good teamwork dynamics and flatter management styles.

6.4.4 Improvements in the Sri Lankan research system

As mentioned previously, Sri Lanka has been increasingly investing in developing scientific research capacity in order to establish itself as a technical research hub in South Asia. The main thrust for this came in 2007 through the presidential policy document “Mahinda Chintana: Vision for a New Sri Lanka”, a ten year development framework based on science and technology for economic development which advocates for more commercial clinical trials. Recognising that inadequacies in research capacity were preventing the desired growth a number of improvements have been made. Of relevance to clinical trials are the new research incentives provided to clinicians, and The National Research Council implementing a target orientated approach to its grant funding to more strategically address priority areas. Amongst the top criteria for funding is that research should address national development issues and have a defined pathway from research outcomes to policy [276]. Although only making slow progress, the clinical trial act and a dedicated clinical trial authority are forming, and the recently established Cosmetics Drugs and Devices Regulatory Authority is also finding its feet. While this bodes well for the future of clinical trials in Sri Lanka, the overt emphasis on commercial studies has raised concerns over patient rights, benefits and safety [277].

6.4.5 Strengths and limitations and further work

Although this case-study recruited fewer participants than the Cameroon case-study, data saturation appeared to be reached and a thorough account of the barriers and enablers to locally-led trial conduct was developed. Furthermore, the Sri Lankan study strongly complemented the previous case-studies, strengthening existing findings and providing greater detail. Although no new barriers and enablers were found, best practices were identified in the sense that the Sri Lankan findings helped to clarify and confirm the importance of enablers suggested in previous case-studies. Furthermore, where barriers were weaker in Sri Lanka compared to the other case-studies, and this could be connected to improved clinical trial outcomes, this strongly supports arguments that reducing proposed barriers would facilitate locally-led trials. Perhaps most importantly, the fact that no distinctly new barriers, enablers or mechanisms were identified, despite experiences being drawn from diverse settings, suggests that the overall findings and theoretical framework capture most of the key issues influencing clinical trial conduct. As such, although the relative presence or absence of these influences are clearly variable, that they are important for locally-led trial conduct appears potentially generalizable.

However, despite Sri Lanka being a fairly different research context to Ethiopia and Cameroon, many structural factors and even work cultures were similar. Therefore it is possible that no new barriers and enablers and mechanisms were found because there were fundamental similarities in the research context. While it is possible that these factors are simply common to many LAMICs and the theoretical framework would therefore be widely generalizable, further examination of the prevalence of the identified key factors is needed.

To achieve this, the following chapter will closely compare the case-study findings with those from the literature synthesis. Since the literature synthesis draws from experiences, opinions and evidence from a large variety of LAMICs, this should prove sufficient to identify if the theoretical framework developed in this thesis has wider importance beyond the case-study countries. Furthermore, because the literature synthesis investigated all health research capacity development, not just clinical trials, the relevance of this study's findings to general health research may be considered. Based on this wider interpretation of the thesis findings, a holistic theoretical framework detailing recommendations for facilitating locally-led trial conduct in LAMICs will be developed.

PART IV: DISCUSSION AND CONCLUSIONS

Chapter 7: The antecedents and consequences of locally-led trial conduct

“Science cannot be given; it should be taken”: - Secretary General of the UNESCO/ICSU; World Conference on Science, 2004 [13]

7.1 Introduction

This thesis has described in detail key issues influencing locally-led trial conduct in LAMICS through three case-studies in Ethiopia, Cameroon and Sri Lanka. Overall, the results show that there is no single issue inhibiting locally-led trial conduct. Rather, inter-related deficiencies at all levels of the research system need to be addressed for locally-led trial capacity to be sustainably developed.

At the macro-level, clinical trial research requires greater prioritisation in terms of the resources available for health research and strengthening of support structures so that trial operations can be improved and research activities lead to high-quality and impactful research. This will require: streamlining governance and administration and fostering an appreciation for evidence-based-medicine and trials so that research is supported rather than hindered; better coordinating and aligning

of existing capacities through developing research strategy and encouraging networking; strengthening policy capacity to demand and use research and interact with research producers so that trial research focuses on producing useful outputs and can lead to improved health outcomes; and building regulatory capacity to effectively, efficiently and safely oversee trial activities.

At the institutional level there needs to be greater support and encouragement of clinical trial and research conduct and increased attention to developing the human and material resources to allow this happen. This will require providing more theoretical and practical learning experiences to develop the pool of human resources with the capacity to work on and lead trials, as well as incentivising and mainstreaming clinical trial research within institutions so that existing expertise is effectively utilised. At the same time, local system-based institutions need to develop their material research capacity and support services so that the conduct of high quality clinical trials is a feasible and attractive option.

At the individual level, the existing trial leaders and staff have a critical role in developing a future generation of research leaders, supporting institutional capacity building, and driving a movement towards valuing evidence-based medicine so that clinical trials become more valued. This will require fostering pro-research cultures through knowledge sharing and mentorship; providing comprehensive practical trial experiences and supporting the professional development of junior staff; attempting to strengthen collaboratory and team working attitudes; working more cohesively with all stakeholders within the local research system; and acting as champions of trial research by conducting impactful trials and advocating for increased investment.

This final discussion chapter will focus on summarising and then bringing together the case-study findings and literature within a carefully considered conceptual framework for locally-led trial capacity development. This will situate the findings within the context that they came from, but at the same time draw out more general lessons that are relevant for developing locally-led trial and health research capacity in LAMICs, thus making the findings from this thesis more widely useful.

This conceptual framework will then be used to produce practical and action-orientated recommendations for facilitating the conduct of locally-led trials in LAMICs. By basing these recommendations on the conceptual framework and the theories of change within it, it will be possible to understand which recommendations are more widely generalizable, and which are only useful for specific contexts. The goal of this is to provide a useful planning tool for development strategies in any LAMIC context, so long as development actors have a good understanding of the context they are working in.

The strengths and limitations of the conceptual framework and recommendations will then be assessed with reference to other research capacity development guidance documents. Finally, conclusions will be presented and potential future work proposed.

7.2 Summary of the results chapters' findings

Conceptual models and theoretical frameworks exploring and explaining the findings in each case-study have been presented. Interpretations from the Cameroon case-study were developed through comparison and learning from the Ethiopian case-study, and interpretations from the Sri Lankan case-study were developed through comparison to both previous case-studies.

This iterative learning and comparison suggests that although the occurrence of barriers and enablers vary within and between research contexts, this thesis has identified many key issues, influential mechanisms, and limiting factors influencing locally-led trials in LAMICS. However, it is still not clear if the theoretical framework is widely generalizable to LAMIC research contexts, or if other mechanisms are important in settings with more fundamental differences in their research system organisation.

The systematic literature synthesis of health research capacity development in LAMICs provides a broader context to expand on the interpretation of these results and understand if the findings from the case-studies can be applied to other LAMIC settings and health research more generally. To demonstrate the commonalities and divergences between the case-study findings and the literature, Table 7.1 summarises and integrates the key findings from the three case-studies and the literature synthesis according to the recognised elements of the research system; stewardship and governance, financing, creating and sustaining resources, and producing a using research [74].

Table 7-1 Comparison of key findings between results chapters and literature synthesis

Green tick indicates issues are the same, orange tick indicates issues are the same with minor exceptions where some issues are not mentioned or identified, red tick indicates some issues are the same but several points are not mentioned or identified. There were no contradictory findings.

General situation in LAMICs as represented by the summarised and integrated findings from the four results chapters	Comparison of findings between results chapters			
	Ethiopia	Cameroon	Sri Lanka	Literature synthesis
Stewardship & governance				
Inefficient governance - Largely bureaucratic, centralised hierarchies & strongly formalised organisational management structures leads to complex, multiplicative governance & permissions & fragmented strategy. Hierarchies & bureaucracy can lead to administrative not research based leadership promotion, poor performance norms, counter-productive non-trusting or competitive professional relationships, & resistance to streamlining, bottom-up initiatives, & delegating responsibility.	✓ Hierarchies not mentioned, but reported present in literature	✓	✓	✓ Factors rarely attributed to hierarchies
Weak research stewardship; lack of strategy leads to supply-led, largely academic research & fragmented evidence of limited use for policy. Priorities may exist but limited local funding means agendas often foreign-led, sometimes inappropriately. Decision-makers may lack knowledge or appreciation for research due to administrative promotion. This de-values local research, prevents research cultures & results in suspicion & blocking of research. Greater national investment & strategy required. Situation slowly improving due to local & foreign commitments.	✓	✓	✓ Research appreciated and strong research cultures in academia	✓ Provides greater detail on guidance and international roles
Bureaucratic administration; introduces operational delays & permits low performance norms. Requirement for multiple permissions slows operations & encourages research “blocking”. Financial regulations inhibit purchasing. Lack of research services, little appreciation for administration, & poor research-administrator engagement increase problems. This frequently results in researchers setting up parallel structures to bypass local systems. To overcome this, performance targets with clear accountability, institutional capacity development to manage research, & closer engagement needed.	✓ Administration problems reported but no solutions offered	✓ Some corruption also reported	✓ Parallel structures rare as most research locally-led & institution-based	✓
Weak regulatory frameworks; have limited review & monitoring capacity, are overly complicated & cautious, & lack legal backing. This slows review times, limits scope of trials permitted & fuels ethical concerns. Poor quality applications also cause delay. More training in research ethics & trial design needed for reviewers & researchers. Committees need greater resources & legal backing. Increasing government commitment needed.	✓	✓	✓	✓ Greater detail on developing regulatory and ethical review frameworks

Financing				
Research priority and finances for research - Little top-level appreciation for research & EBM. Universities prioritise teaching over research & research cultures often lacking. Investigators forced to apply for international funds but success is rare. This reduces the quantity & scope of research or makes them dependent on foreign collaboration. To increase the value of research, advocacy of research benefits is needed. To gain international grants, skills in writing quality research proposals & international partnership are needed. Small research grants may support local studies.	✓	✓	✓ Low value national grants available. Research strongly supported in academia and commercial trials valued. Little dependence on collaboration except for international grants.	✓ More detail on funding strategies
Creating and sustaining resources				
Limited material capacity particularly in laboratories; limits the scope of trials that can be attempted, may prevent collaborations & means samples may have to be analysed abroad. Basic services are also problematic. Few journal subscriptions & poor internet limit information & communication access. Resource constraints reduce motivation & self-efficacy. Greater institutional investment needed.	✓	✓	✓ Basic services & internet generally not problematic	✓
Lack of human capacity to conduct research generally more limiting than material resources; due to lack of skilled personnel but also ineffectual use expertise. Skills gaps blamed on little research training in education & work, few knowledge resources, few research opportunities & limited mentorship. Effective use of human resources prevented by: limited time, few research careers, low motivation, poor research environment, intellectual isolation, limited teamwork & collaboration. This can lead to brain drain.	✓	✓ Material resources perceived as more limiting than human. Expertise may be ignored.	✓ Local researcher isolation not problematic. Brain drain not mentioned.	✓
Developing human resource capacity is critical to increasing research conduct. Knowledge & skill development modalities include: research modules in curricula, work-based training, trainer-of-trainer programmes, e-learning, networking & knowledge sharing, & mentorship. This also inculcates research culture by increasing exposure, motivating personnel & increasing self-efficacy. Didactic training alone not normally sufficient to initiate trials so practical experience is needed to increase technical skills, leadership capabilities, & self-efficacy.	✓	✓	✓	✓ Benefits for motivation and self-efficacy less mentioned
Trial experience is the best learning & development strategy; it gives exposure to trials & new methods, raises standards, & increases skills. FIT experience preferred for developing technical skills, knowledge sharing, & easier operations. But procedural nature & lack of inclusion & autonomy frustrates researchers. Locally-led trial experience normally better at developing leadership capacity due to opportunities for responsibility and challenging work because improves learning, self-efficacy & motivation. Embedding trials important for developing institutional capacity. Strong teamwork dynamics improves learning.	✓	✓	✓	✓ Responsibility, challenging work and teamwork rarely emphasised.

Awareness of trials & exposure to research important for thinking about research conduct, inculcating a research culture & securing stakeholder buy-in. This reduces suspicion of trials & increases the value of research. Exposure to trials & research is limited by minimal research training, little knowledge sharing & mentorship, limited access to knowledge resources & few trials conducted. Conducting & seeing research, sharing experiences through departmental events, teaching research, & mentorship can increase exposure.	✓ Exposure reducing suspicion not mentioned	✓	✓ Exposure not needed for academics	✓
Low motivation to conduct research prevents interest in trials & effective use of expertise. Difficult operations, few incentives, little time, few research careers, poor research environment & expectation of barriers were disincentives. Career recognition & professional development was as important as financial incentives if research was linked to valuable career progression. If not, salary incentives are normally a prerequisite for motivation. However, intrinsic incentives such as responsibility, recognition and challenging work sometimes off-set this.	✓ Responsibility & challenging work not mentioned	✓	✓ Better incentives for academic vs healthcare staff caused relationship difficulties	✓ Little attention to weighting of factors & responsibility and challenging work
Producing and using research				
Difficult operations reduce trial conduct & usefulness for policy; operations are similar for most trials but task difficulty varies depending on severity of barriers & enablers. Start-up stage normally most difficult. Expectation of barriers reduces motivation & self-efficacy. Leadership capabilities & collaboration & teamwork help cope with barriers, but resolution is dependent on system-wide development.	✓	✓	✓	✓
Low uptake of research for policy. Fragmented research, limited scope & supply-driven academic research reduce usefulness of trial evidence. Limited appreciation & understanding of research by decision-makers reduces evidence use. Little researcher-policy engagement & poor dissemination reduces research impact. This reduces perceived value of local research. Evidence-based guidelines often have little impact due to resistance to EBM or poor delivery. International evidence has more impact than local because of international backing, credibility & greater availability. Greater research-policy engagement & capacity building needed.	✓ Few evidence-based policies & research of questionable use, but little other detail mentioned	✓ Efforts to address this, especially research-policy engagement through platforms.	✓ Uptake depends on policy programme. Preference for international evidence not mentioned.	✓ More guidance provided.
Self-efficacy to conduct trials is an important for trial undertaking & leadership. Researchers frequently lack self-efficacy to lead studies even if they have extensive previous foreign-trial experience. Self-efficacy is reduced by: perceived complexity of trials, limited knowledge, little exposure to trials, lack of support, & lack of responsibility and openness to bottom-up initiatives. Self-efficacy increases through: training opportunities, trial experiences, mentorship and support, exposure to successful trials, responsibility & ability to make contributions.	✓	✓	✓ Self-efficacy not problematic for academics	✓ Rarely mentioned

Local collaboration & teamwork important for enabling trials by: pooling resources to reach a critical mass, improving relationships with stakeholders, building team morale, encouraging knowledge sharing, facilitating operations, & making research more useful for policy. However, local collaboration & teamwork are rare. They are prevented by limited networking & poor professional relationships & preference for HIC partners. Collaborative & teamwork are strengthened by: strategic networking & issue selling & team leadership skills.	✓ Teamwork and issue selling not mentioned	✓	✓	✓ Mostly only regional and international collaboration mentioned
International collaboration enables research. However, capacity development varies. Longer-term partnerships usually better because they have greater local inclusion & teamwork dynamics. Most international collaborations develop parallel structures which limit local institutional development. To ensure beneficial partnerships, strong local leadership is essential.	✓	✓	✓	✓
Networking is important for forging local & international collaborations, building professional relationships & teamwork, & engagement with stakeholders. International networking is more established than local networking due to preference for international partners. Networking is prevented by not having formal contacts, not being aware of expertise & poor professional relationships. Networking is improved by mapping expertise into registries, networking events & tools. Interpersonal skills especially issue selling help forge relationships.	✓ Skills in forging relationships not mentioned	✓	✓ Local expertise generally well known, so mapping less important	✓ Skills in forging relationships not mentioned

This table clearly shows the common elements and modest differences between the case-studies. The case-study findings also have strong similarities with the main issues discussed in the literature. Importantly, there were no contradictory findings. Since the literature includes author contributions from all over the world discussing capacity development for various types of health research in many LAMICs, this strongly indicates that many of case-study findings are widely generalizable LAMIC research contexts. It also suggests that many of the issues facing locally-led trial conduct are similar to the issues faced when developing local capacity to conduct other types of health research. As such, the findings from this thesis are likely to be of relevance to most types of health research in LAMICs, not just clinical trials.

However, several of the case-study findings appear largely novel, which either means that they are specific to the case-country contexts, or they are previously unidentified issues. Furthermore, although the findings from this thesis have similarities to issues in the literature, the majority of contributions were not empirical, did not relate to specific contexts or only related to a single context, and did not have a specific focus on clinical trials, especially locally-led. Therefore even when similarities with the literature are shown, this thesis's findings remain largely empirically novel and one of the most detailed and strong contributions to the health research capacity development literature.

7.3 Antecedents and consequences of local-trial undertaking

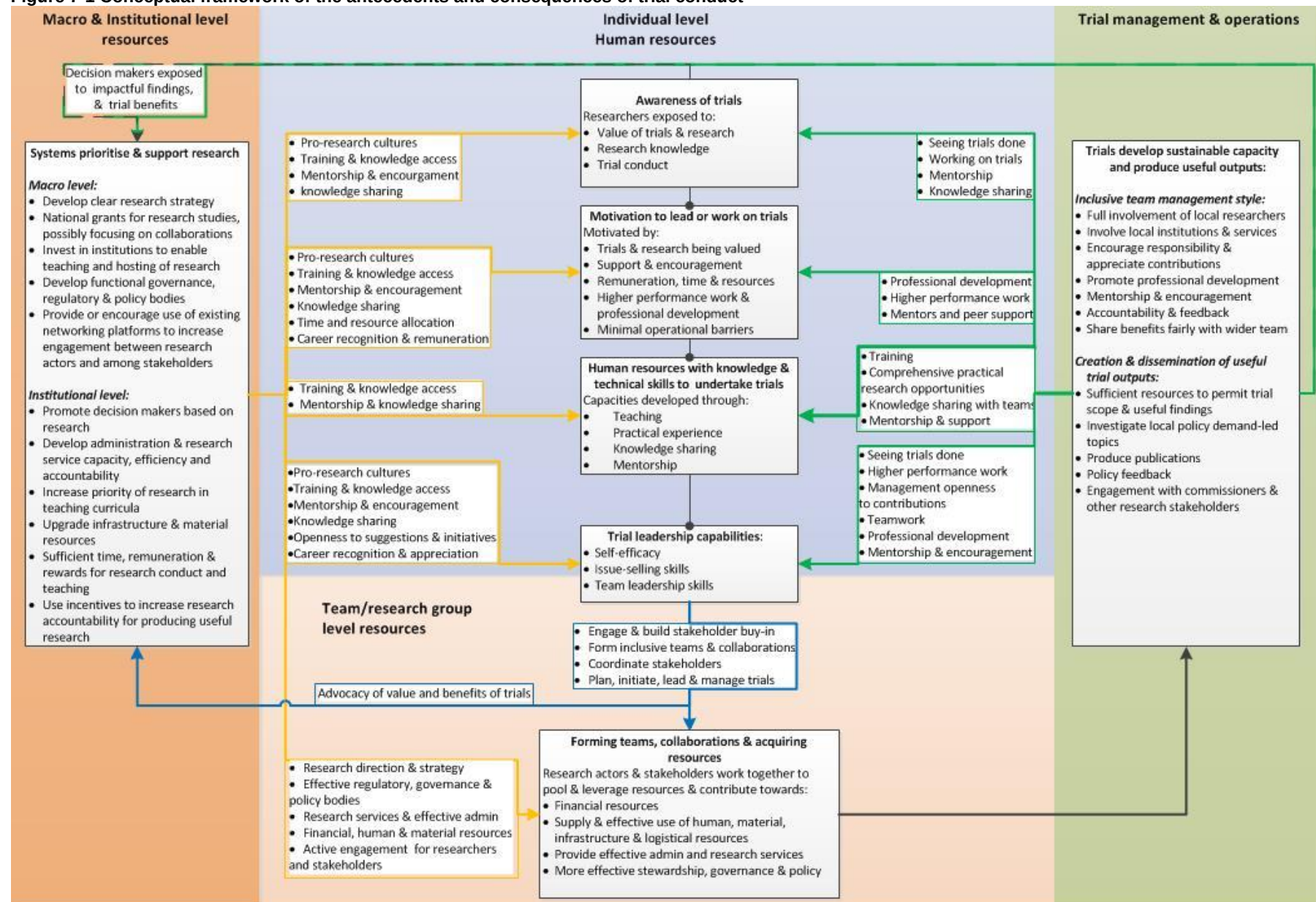
This section presents the findings from all three case-studies as a combined conceptual framework of antecedents and consequences of locally-led trial undertaking.

Figure 7.1 shows the important components of the antecedents, the drivers of the antecedents, and their consequences on trial operations and conduct. The

antecedents identified from across the cases are: awareness and appreciation for health research and clinical trials; motivation to conduct clinical trials; availability of human resources with trial knowledge and technical skills; research leadership capabilities; ability to form collaborations, effective teams and acquire resources; trial management dedicated to sustainable capacity development and producing locally useful research; and system-wide prioritisation of health research.

The following sections explain the importance and evidence for the antecedents and their drivers in detail, and contrast them with what is currently being delivered, according to the case-studies. Where components in the framework are supported by capacity development literature, citations are provided to show the wider support for these arguments. However, as mentioned previously, it is important to note that the majority of this literature does not specifically relate to clinical trials, and is not empirically backed. Furthermore, only 3 papers were dedicated to locally-led trials, and none of their contributions were empirical. Therefore, where this thesis's findings agree with the literature, it often provides the first empirical evidence to the claims previously made.

Figure 7-1 Conceptual framework of the antecedents and consequences of trial conduct



7.3.1 Developing awareness and appreciation for health research and clinical trials

There was wide agreement between all the case-studies that greater awareness of trials and health research is needed to foster more pro-research cultures and thereby propagate locally-led trial undertaking. The concept of awareness, as described by participants, encompassed two main aspects.

Firstly, an overall understanding of the concept of modern biomedical research was thought to be important for developing a future cadre of health researchers with a positive and interested attitude towards clinical trials and health research more generally. This included understanding: the principles of biomedical research; health research methods such as how clinical trials are conducted and what they involve; their purpose (e.g. testing hypotheses and answering a research question rather than providing therapy to patients); and ethical principles designed to ensure the safety of patients.

The second aspect of the concept of awareness was about promoting or advocating for the potential value of clinical trial evidence for improving patient care so that potential researchers would desire to conduct trials and decision-makers would direct funds and support towards them. In many case-study institutions, especially healthcare, practitioners and decision-makers often did not appreciate that evidence-based medicine could improve patient care or were resistant to it on the grounds it could limit their autonomy in treating patients. Overcoming this disinterest or resistance to health research and evidence-based medicine was reportedly critical for ensuring a more positive research culture and securing the allocation of resources to allow more research, especially clinical trials. As such, awareness activities that could convince individuals of the legitimacy of evidence-

based medicine for improving population health, and the superior value of clinical trials for contributing to the evidence base were reportedly needed.

The importance of vibrant local research communities [15] for encouraging new [104 ,122 ,172 ,174] and established researchers [30 ,84 ,91] to undertake health research is present in the literature. However, these specific arguments on the importance of trial and biomedical research awareness for developing pro-research cultures and securing political support are novel within the literature. They are, however, supported by the ADKAR model for change [240] (presented in section 4.5.3 page 154) which argues that for a change to be successful, individuals must understand the components of a change, internalise why it is important, and desire for the change to take place.

To engender more awareness, greater exposure to trials is needed. However, exposure to any biomedical research would likely be helpful because it primed individuals' interest for trials. Suggested exposure methods included: increasing research and clinical trial modules in university curricula [178 ,198], mentorship [198], knowledge sharing [195] events such as seminars and workshops [194] [190] training courses and access to knowledge resources [26 ,51 ,154] and opportunities to work on trials [55 ,178]. Given the presence of these arguments in all case-studies and HRCD literature, this seems largely generalizable to LAMICs. Seeing trials conducted within individuals' own institutions was important in all case-studies, but was not identified in the literature. However, this is an important finding because it provides further support for arguments that clinical trials should be conducted within local institutions. Consideration of how this can be implemented is presented in sections 7.3.6 (page 322) and 7.3.7 (page 328).

7.3.2 Increasing motivation to conduct trials

Personal motivation for research leaders and staff to conduct trials and health research was a very important theme in all case-studies and the literature [8 ,26 ,73 ,113 ,170]. This was because for most potential health researchers, research is a discretionary activity that they can choose to undertake, usually alongside many other duties and priorities. All the case-studies and literature agree that for research to be a priority activity, intrinsic and extrinsic incentives are required [26 ,73 ,83 ,125 ,195]. If these incentives are not present, individuals are unlikely to volunteer to work on or undertake trials [170]. Alternatively, participants in Ethiopia and Cameroon reported that researchers may choose to work in other external national [5 ,40] or international institutions [7 ,177] that provided better incentives, resulting in brain drain from local institutions [27 ,30].

Within dedicated research institutions and Sri Lankan academia where research was required for career progression and supported through providing time, incentives and resources for research, potential researchers willingly conducted trials and health research. However, for academic institutions in Cameroon and Ethiopia, and healthcare institutions in all case-countries, low motivation to conduct research was apparent and blocked the undertaking of trials. Participant reasons for this matched opinions expressed in the literature: few financial incentives for conducting research, research was not appreciated [73] or recognised [36 ,41 ,84], and progression in research careers did not lead to relatively better financial rewards and working conditions than not conducting research [7 ,30 ,118]. As such, research was a part-time or irregular side-activity which needed to compete with private practice and other activities [26], but frequently failed to do so because of poor incentives. This situation was exacerbated when individuals had little allotted

or practically implemented time for research [234 ,242 ,[55 ,174]. Perceptions that trial operations would be difficult and time consuming [24 ,43], negative attitudes towards research [72 ,130] and lack of peer support [35 ,152] further decreased motivation to conduct trials. Therefore, health research was often an unfavourable career choice [73 ,113]. Potential researchers in healthcare institutions had the lowest motivation to conduct trials because research was not linked to their career progression and negative attitudes to research were common.

To increase motivation, there was wide agreement in all case-studies and the literature that the following incentives are required: financial remuneration [26 ,125], career recognition [119 ,197], adequate resources [50 ,83], dedicated time [125], minimal operational barriers [24] and a pro-research environment that requires or encourages research [104 ,172 ,174]. Cameroonian participants said these incentives were especially important for individuals returning from study abroad to prevent their brain drain, which agrees with the literature [197] [142]. However, reports from Sri Lanka that differential incentives for academics and healthcare staff led to relational problems, suggests that research incentives must be implemented with care.

However, some employees in all case-countries still chose to conduct trials despite few incentives. The motivation for these “unconventional” investigators was driven by the desire for personal and professional development, opportunities for responsibility, challenging work and international or peer recognition. The importance of responsibility and challenging work for motivating research is novel within the HRCD literature. However this is strongly supported by the motivational theories presented in the chapter 5 discussion (section 5.5.2 page 219) which suggest these particular intrinsic motivators are important for individuals who have

a strong desire to take on new roles and responsibilities, master skills, and progress in their career (high “growth need”). Therefore it is likely that in addition to widely recognised “conventional” incentives, provision of career “growth need” motivators is important, especially if other incentives are in short supply. However, since these issues were not identified in the Ethiopian case-study, further research into this is required. Consideration of how both conventional and career “growth need” incentives can be provided is addressed in sections 7.3.6 (page 322) and 7.3.7 (page 328).

7.3.3 Developing human resources with trial knowledge and technical skills

Even if the extant human resources capable of conducting trials are used more effectively, there was wide agreement in all case-studies and the literature that more human resources with the skills, knowledge and capabilities to lead and work on trials are needed [54]. Indeed participants from Ethiopia and Sri Lanka, and authors in the literature [25-27], argue that this is one of the greatest barriers to trial conduct.

In all case-studies, participants were of the opinion that if more academics and frontline healthcare staff had trial knowledge and skills, then more trials could be conducted, assuming skilled individuals were willing to work on them. This was because both locally-led and foreign-led trials were prevented by insufficient availability of trial competent staff. The reason there was such a limited pool of trial expertise to draw upon was that with the exception of Sri Lanka, trial learning opportunities were rare, often opportunistic, and always competitive.

All case-studies and the literature were in agreement that opportunities to develop trial knowledge and skills were reduced by limited attention to research methods in undergraduate curricula and continuing education [26 ,169-171],

especially in healthcare fields. An overreliance on didactic teaching methods [130] and insufficient access to literature and other knowledge resources also inhibited trial learning possibilities [26 ,51 ,154]. Within Ethiopia and Cameroon, few opportunities for trial mentorship, knowledge sharing [26 ,55 ,154 ,174 ,175], and work experiences [55] especially in more advanced roles [105 ,113] further reduced the possibility of developing a pool of trial competent human resources.

This situation caused a number of gaps in biomedical research skills that participants in all case-countries and authors in the literature regularly cited as being required to successfully undertake and work on trials: research design [109 ,162 ,207], research ethics [16], good research practices e.g. GCP [55], data management [153], statistics [73 ,112 ,142 ,155], laboratory practice [85 ,110], and writing for grants and publication [10 ,28 ,48]. These skills gaps made it difficult for local researchers to compete for international grants [83 ,174] and gain research permissions [16], reduced human resources available for trial research [19], and inhibited research dissemination [54] and impact [17 ,21 ,28 ,48].

To overcome these skills gaps, all case-studies and the literature agreed that biomedical research needed greater presence in university curricula [105 ,119 ,157]. Although trial teaching would be most effective, learning the general principles of modern biomedical research was also needed [178 ,198]. In the Sri Lankan case-study this was deemed the most critical factor for developing human resources. Additional top-up training courses covering specific aspects of research and clinical trials would also be very helpful [55 ,73 ,85 ,110 ,112 ,142], but limited funding and time could make attendance difficult, especially if travel was required [157]. Cameroonian and Ethiopian participants emphasised that training needed to be regular and relevant to local contexts [83 ,142], which meant train-the-trainer

approaches would be important [7 ,55]. However, in all case-studies, capacity to teach research, especially clinical trials, was limited. Therefore to be implementable, greater resource allocation and staff development is required.

To enable healthcare and academic professionals who had an interest in conducting research and trials to pursue independent learning, more knowledge resources were needed. Almost all good examples cited were provided internationally. For ease of access, internet based resources such as open-access journals [53 ,206] and e-learning [36 ,98 ,119] were preferred, despite reported lack of access to internet [27]. HINARI was widely cited as an extremely useful resource, but many participants reported intermittent availability. In response to these demands, The Global Health Network [212] began providing comprehensive e-learning modules on clinical trials that are tailored to be relevant for resource-limited settings. They have also recently released a global health research Process Map that guides researchers through the stages of running research projects, including clinical trials, in resource-limited settings. These tools were recently applauded in The 2013 World Health Report [1] and Nature Medicine [278] for improving LAMIC access to essential research knowledge.

Although teaching and learning resources can develop an understanding of trial and health research methods, in all case-studies practical trial and health research experiences [10 ,19 ,178 ,208] and work-based knowledge sharing with peers and mentors [75 ,182] were essential for developing technical skills through learning by doing and participating in communities of practice. As explained in section 5.5.3 (page 226), this is because the ability to perform tasks and achieve goals is learnt through the process of doing and activity and observing and participating with the actions of peers and seniors who are also knowledgeably undertaking the activity.

To be most effective these trial experiences needed to allow staff to be fully involved in all aspects of trial conduct, provide comprehensive training and professional development, and offer peer support and mentoring within trial teams. However, in Cameroon and Ethiopia, such trial work opportunities were scarce. As such, lack of effective practical learning opportunities was considered to be one of the main barriers to the development of human resources for trials.

Given the importance of providing theoretical and practical training in all case studies and much of the literature, these issues appear generalizable to LAMICS. Consideration of how to increase their provision will be addressed in sections 7.3.6 (page 322) and 7.3.7 (page 328).

7.3.4 Forming collaborations, effective teams and acquiring resources

The importance of collaboration for enabling the conduct of locally-led trials was reported by many trial teams in every case-study. This was because collaboration supplied, aligned and leveraged the essentially required resources and logistics for trials to be successfully operationalised [3 ,125 ,148 ,200].

International collaboration was very helpful for enabling research that was beyond local capacity constraints [16 ,31 ,80]. In Cameroon and Ethiopia where local resources and funding were minimal, collaboration with foreign groups was near essential. This was because foreign collaborations provided finances, access to material and human resources and expertise, capacity development, logistical and administrative support, and credibility and support with applications [3 ,31 ,40 ,125 ,200]. Indeed in all case-studies, successfully gaining international funding was almost always associated with foreign collaboration or assistance.

However, local collaboration was also very enabling when it was achieved because it could bring disparate local resources together to reach a self-sufficient

critical mass. Collaborations that went beyond research-producers were also extremely helpful [10 ,34 ,36 ,74 ,120 ,203]; working with hospitals, schools and ministries permitted pooling and sharing of resources such as staff, transport and laboratory facilities [28 ,73]. Functional relationships with administration departments [3 ,50], governance bodies [3 ,50], research strategy actors [17 ,75] and policy-makers [62 ,156] also greatly helped improve the efficiency, usefulness, and impact of research.

Although some trial teams groups were successful in forming international collaborations, respondents from all case-studies commented that this was difficult due to a lack of networking opportunities and contacts, insufficient capacity to attract collaborators, or local research topics being of little international interest. Perhaps surprisingly, given the international focus on collaborative partnerships, there is little recognition in the HRCD literature of the difficulties LAMIC researchers face when trying to initiate collaborations. In Cameroon and Ethiopia, desperation for foreign-collaboration meant local investigators were in a vulnerable negotiating position [5 ,53 ,99] and therefore may accept exploitative terms or menial roles [33]. International funding contingent on working with HIC research groups exacerbated this. As such, although foreign collaboration was important for getting research done, it did not always conform to ideals of benefiting local researchers and developing capacity [33 ,46 ,97] (see section 7.3.6 (page 322) for further details).

One tool that was designed to overcome some of these international collaboration issues is SiteFinder, hosted by The Global Health Network [212]. This is a novel networking application and database of HIC and LAMIC research groups that allows potential collaborators to learn about each other's projects and sites. By giving LAMIC researchers greater access to international contacts in an open and

transparent forum, the hope is that can be more selective about the projects they accept and only agree to mutually beneficial research. There are also an increasing number of guides designed to help LAMIC researchers negotiate with foreign partners [33]. Consideration of how the local research system can support greater networking is addressed in section 7.3.7 (page 328).

Forming broadly inclusive local collaborations was very difficult, and teams that achieved this were often only partially successful at including all the necessary actors and stakeholders. Including other research groups and strategy and policy actors was particularly difficult and rare. Although this was partly due to the limited capacity of research producers and stakeholders, even when they were present and functional, poor local networking, communication, and strategic direction prevented their effective use and incorporation into collaborations [28 ,93 ,150]. Researchers were often unknown to each other, as well as commissioners and users of research [73]. This prevented collaboration on more ambitious projects, as well as demand-led research and policy uptake [25 ,32 ,154]. Regulatory, ethical and administration departments sometimes had clear procedures and could offer helpful support for researchers, but a lack of clear engagement strategies prevented this [139]. Overall this meant local research systems were fragmented and resulted in isolated research that often lacked sufficient scope to be useful [4 ,10 ,24 ,30].

Although building capacity of local research stakeholders and providing better communication through networking platforms should help, these interventions are unlikely to increase local collaboration unless relations between actors and stakeholders improve and they become better at collaboratively working together towards common goals. In all case-countries research producers rarely collaborated, not just because of isolation but also because of individualistic and

competitive attitudes. Such attitudes also appear common in other LAMICs [35 ,152]. In Cameroon this was most severe and could result in colleagues deliberately undermining research efforts and not supporting colleagues. Relationships between clinicians and academics were particularly problematic, and in all case-countries decision-makers and administrators either being suspicious or disinterested in trials prevented cooperation and caused operational delays [72 ,130]. Furthermore, although Cameroonian policy-makers had developed an engagement platform, local researchers still failed to use it.

Although these professional divisions were partly caused by a lack of common goals or appreciation for research, they were exacerbated by hierarchical structures, differential incentives, and individual level competition for limited rewards and opportunities. Although these findings are supported by research on organisational team working [266 ,274] (see section 6.4.1 page 281), these explanations for poor collaborative attitudes are largely novel within the HRCD literature, and therefore warrant further research to explore these issues in greater depth.

This all suggests that if a more holistic research system is to be developed where all research stakeholders work together towards common goals, cooperation should be encouraged, research governance needs to be harmonised in terms of buy-in and incentives for research, and rewards and opportunities should be based more on team efforts than individual performance. Encouragingly both Cameroonian and Sri Lankan governments had started providing incentives for clinicians to conduct research. However, breaking down long-standing negative research cultures in healthcare institutions and widespread anti-collaboratory attitudes may require more than just fairer research incentives. As such, further research is required to

better understand how academic and healthcare professional identities are reinforced or can coalesce, and the impact this has on health research collaboration and team working dynamics.

Despite these relational problems, some participants were successful in forming local collaborations and teams, and forging good relationships with research stakeholders. When referring to collaborations and teams, participants were very inclusive in what they considered to be an optimal team. Indeed, their description of teams included broad stakeholders: project leaders, local or international collaborators, policy bodies and governance structures, administrative support, as well as trial staff such as data collectors and laboratory personnel.

In all case-studies, the key to developing these relationships was having research leaders who could develop trusting relationships and establish common goals with key stakeholders and potential collaborators and team members. This was achieved through local trial investigators credibly emphasising the value of trial research for all parties and establishing quality communication through regular information sharing. Although the provision of this information is similar to providing awareness, according to Sri Lankan and Cameroonian participants, successful delivery of this information required a much more personal, active, diplomatic and strategic process akin to “issue selling” theory [267] (presented in section 6.4.3, page 290). Consideration of how these “issue selling” leadership skills are developed and can be encouraged is addressed in section 7.3.5 (page 319) and 7.3.6 (page 322). Several trial teams in Cameroon and Sri Lanka said that in addition to collaboration, good team working was important for improving overall performance. Their conceptualisation of good team working involved all team members work together towards common goals and helping each other, sharing

work burdens and cooperating, sharing knowledge, offering suggestions and opinions, showing more initiative and taking on extra responsibilities. This was important because when “good” team working was achieved it reportedly: improved trial operations, increased motivation and staff performance, created a culture of excellence, and reduced staff turnover. Furthermore, as suggested in section 6.4.3 (page 289), the more open and sharing environments that team working fostered should also help develop “communities of practice” [182] during trial operations, which would support learning from colleagues and the sharing of tacit knowledge, which is essentially the “how to” tips needed to iteratively improve trial operations.

The creation of these high performance research team cultures was attributed to the actions of research leaders who exhibited reportedly good team leadership skills through adopting inclusive, flatter management styles. Although participants did not state that such flatter management styles could not develop in hierarchical organisational structures, literature on labour theory suggests that less hierarchical organisational structures are more conducive to teamwork and employee cohesion [274]. Therefore, within the specific context of research teams where team working and employee cohesion was valued, it seems likely that inclusive management and flatter hierarchies were advantageous. Consideration of how these team working skills are developed and can be fostered within a research team context is addressed in section 7.3.5 (page 319) and 7.3.6 (page 322).

Although, Ethiopian participants did not state that team working was important, a report on required capacity building for Ethiopian universities strongly suggests that more team working and improved cooperation is important [220]. With the exception of this internal report from Ethiopia, the importance of teamwork for research operations is novel within the HRCD literature. However, overall, it is clear

that collaboration is of generalizable importance in LAMICs and there is strong evidence to suggest that good team working can improve the performance of research projects.

7.3.5 Fostering research leadership capabilities

The findings from all case-studies clearly indicated that in addition to trial technical skills and knowledge, successful trial undertaking required certain leadership capabilities, namely self-efficacy, ability to strategically “sell issues”, and good team leadership.

Self-efficacy was considered very important for trial leadership in all case-studies. This is because self-efficacy gives investigators the confidence to lead trials in the face of operational barriers and challenging environments, and supports behaviours which help individuals to cope with these challenges; persistence, reacting positively to setbacks, and negotiating and interpersonal skills.

Self-efficacy was developed through: seeing trials being successfully conducted; receiving training and increasing knowledge; trial experience, particularly opportunities for responsibility and challenging work; and opportunities to make contributions and be listened to. These findings are strongly supported by theories on self-efficacy [251-254] that suggest that self-efficacy is important for developing the “can do” mind-set required for undertaking and successfully completing jobs that involve expanded performance beyond routine duties [251] (section 5.5.2 page 221). Surprisingly, despite its importance in all case-studies, only 1 paper in the HRCD literature mentions confidence as important for leadership [19 ,147 ,176], and it does not consider how it enables research, nor how it is developed. Therefore these findings are largely novel. However, that they were identified in all case-

countries suggests that self-efficacy is likely to be generally important for health research in LAMICs.

The ability to strategically “sell issues” was considered highly enabling to research leadership in the Sri Lankan and Cameroon case-studies because it could help develop productive relationships, forge collaborations and bring all the necessary stakeholders into cohesive teams with a common goal, and secure institutional buy-in and investment in research. In accordance with “issue selling” theory [267] (see section 6.4.3, page 290) this was achieved through active and strategic negotiation techniques that effectively communicated the objectives of trial research and its benefits to encourage institutions and individuals to support and get involved in trials. As such, these skills are also likely to be important for helping research leaders to advocate for clinical trial and health research investment by fostering a movement towards valuing evidence-based medicine.

Although it was unclear how participants learnt their issue selling skills, supportive teamwork environments that valued staff contributions were important for helping people to feel comfortable and confident enough to initiate “issue selling”. However, the importance of these issue selling skills for research leadership is novel within the HRCD literature, and although trusting communicative relationships were important for improving collaboration in Ethiopia, Ethiopian participants did not mention how this was achieved. Therefore further research is required to establish the general importance of issue selling skills.

Team leadership skills were considered important in Cameroon and Sri Lanka for fostering team working cultures that made trial operations more efficient, and improving staff performance and development. Furthermore, they also appear important for making people feel comfortable enough to develop their issue selling

skills. Rather than being a specific skill, successful team leadership was reportedly achieved through adopting various inclusive and flatter management styles. As presented in section 6.4.3 (page 291), these findings are strongly supported by team working theories [271-273] that suggest teamwork is achieved through leaders being dedicated to staff development, sharing benefits and offering opportunities for career growth, and valuing staff inputs.

Although, it was not exactly clear how good team leadership skills were developed, exposure to good team work environments appeared important [275]. The HRCD literature also considers research leaders to be important for developing future research leaders [27 ,202] by involving juniors in the entire research process [196], exposing them to well-functioning team environments and role model team leaders [220], and providing opportunities to take responsibility within a supportive team environment [31]. Therefore, these arguments appear highly plausible. However, because they were not identified by participants in the Ethiopian case-study and the exact process of team leadership development was vague, further research is required.

However, environments that were conducive to the development of these leadership capabilities were uncommon in Cameroon and Ethiopia and healthcare institutions in Sri Lanka, and therefore unavailable to most potential research leaders, which explains why research leaders were rare. This was because: research institutions frequently did not support or encourage trial undertaking and sometimes discouraged it; few trial were conducted so there were few opportunities to see them successfully conducted; there were few opportunities to gain trial experience, especially with positions of responsibility and challenging work; both institutions and foreign-led vertical projects were reportedly resistant to bottom up

initiatives and local staff making contributions; and teamwork and collaborative research environments were uncommon. Consideration of how to provide environments more conducive to the development of these trial leadership capabilities is addressed in sections 7.3.6 (page 322) and 7.3.7 (page 328).

7.3.6 Ensuring trials develop sustainable capacity and produce locally useful research

The in-country conduct of clinical trials was very important in all case-countries because they could produce high quality data with which to fill evidence gaps and tailor international guidelines [1 ,3 ,9]. However, trial conduct was also critical for developing institutional research capacity. Indeed in Cameroon, some participants considered this development impact to be as important as evidence outputs, and in Sri Lanka clinical trials were actively encouraged as a capacity development, rather than health development tool. However, the ability of trials to achieve these beneficial outcomes was variable and dependent on how they were managed and led. In order to successfully achieve these outcomes it was clear that trials needed to be dedicated to ensuring useful evidence generation and developing the capacity of local institutions and research staff.

In terms of ensuring useful research evidence for policy, most participants in all case-studies and authors in the literature [9 ,36 ,41 ,63] considered the evidence arising from locally-led trials to be most useful for policy and have a greater chance of translation. This is because local investigators would be most likely to investigate locally-important topics, in locally-appropriate ways, and should have the best relationships with policy-makers [40 ,41 ,43].

However, the ability of locally-led trials to effectively do this was limited by a number of factors that are also supported by literature. In all case countries, minimal

research strategy and academic supply-driven research [8 ,25 ,32 ,108 ,111 ,154] made it hard to coordinate research around specific priorities [52 ,149]. Furthermore, the frequently limited resources and support available introduced operational barriers which reduced the scope and quality of research outputs [155]. Even if locally-led trials succeeded in creating potentially useful evidence, many investigators had difficulty influencing policy because they lacked skills or connections for evidence dissemination [10 ,28 ,48], there were limited engagement opportunities with policy makers, and policy makers sometimes lacked capacity or interest to use research, [25 ,30-32].

Contrary to opinions in the literature [40 ,42 ,43] and views of some participants in all case-countries, international collaborations usually investigated locally-important research topics and could sometimes be better than locally-led trials at influencing policy. This was because their research outputs had greater scope, and the expertise, resources and credibility they could dedicate to disseminating research outputs and influencing policy makers. Furthermore, the strong local leadership in long-term partnerships helped ensure research topics were locally-relevant and appropriate. However, this foreign dedication to policy impact was only rarely reported in Cameroon and Sri Lanka, and not in Ethiopia, and then only done by long-term partnerships. Indeed, one common respondent criticism of short-term collaborations was that they often failed to involve local stakeholders in research planning and did not disseminate findings locally. Therefore, although international collaboration outputs could influence local policy, concerns in the literature also appear valid [23 ,40].

These findings from the case-studies clearly suggests that for trial evidence to be valuable, both locally-led and foreign-led trials need to pay more attention to the

usefulness of their research and dissemination and translation of evidence into policy. Early inclusion and regular communication with policy bodies will ensure that the research topics are correctly targeted, and will also help to develop relationships and prior consideration of the research which can speed its translation into policy. At the same time, changes at the macro-level of the research system are needed to support locally-led trials in the generation of useful research outputs. These include: clearer demand-driven research strategies to ensure trial research meets local needs; sufficient funding and resources available for locally-led trials so that trials can investigate research topics within sufficient scope to be useful; training for local researchers in evidence dissemination; and strengthening of policy bodies to demand and use research evidence. Consideration of how this can be achieved is presented in section 7.3.7 (page 328).

Trial work experiences were absolutely critical to the development of human resources with the knowledge, technical skills and leadership capabilities to undertake clinical trials. Furthermore, seeing clinical trials successfully conducted could increase awareness of trial research, develop pro-research cultures, and increase self-efficacy and motivation to undertake trials. Provision of material and financial resources through clinical trials was also often instrumental in developing institutional capacity to undertake trials.

However, for these outcomes to be successfully achieved it is clear that the conduct of trials needs to be managed with capacity development in mind. Trials need to be conducted within local institutions and endeavour to share experiences with all institutional staff so that potential researchers and decision-makers can develop an appreciation for their benefits and better understand what conducting a

trial involves. At the same time, trials need to use as many local staff as possible, involve them in all processes and provide opportunities for responsibility and challenging work so that technical skills, self-efficacy and motivation to lead trials are developed. Encouraging open, sharing and supportive team working cultures during trial operations is also important for fostering team working skills, confidence in issue selling, maximising learning opportunities and professional development, as well as increasing trial productivity. Where material resources and finances are provided, these need to be routed through local institutions so that they retain these benefits after trials finish and develop expertise in administering the provision of research services. If these factors are not considered when conducting clinical trials, local staff and institutions are unlikely to develop sustainable capacity to be able to lead their own trials in the future.

Locally-led trials were generally considered the best model for achieving these capacity development ideals because in the majority of cases they were conducted within local institutions, all trial staff were locally sourced, and therefore there were more opportunities for full involvement, responsibility and ownership of the trial [44]. Furthermore, all material resources and finances arising from the trial were generally managed and retained by the local institution. However, locally-led trials had limited ability to develop capacity in more advanced laboratory techniques because the material resources and training required were not institutionally available [25 ,28], and their limited budgets meant that financial and material resource provision was often minimal. Furthermore, the frequently difficult operations, or perception that this was the case, could reduce motivation and self-efficacy to conduct trials, or encourage local investigators to set up parallel structures or route their research through foreign institutions. Therefore, although

locally-led trials could be very effective at improving human and institutional capacity, the extent of their capacity development was limited by the failure of the local research system to provide the necessary resources and services. To leverage the potential for locally-led trials to be an effective capacity development tool, greater macro-level investment is required.

Long-term partnerships were often reported to provide excellent capacity development because they allowed strong local leadership and inclusion, provided local training and professional development, and had large budgets that could develop material capacity, particularly laboratory resources. Strong team working dynamics and exposure to good research practices and new advanced techniques also helped develop a culture of excellence, technical capacity [3 ,45 ,113 ,126], and leadership capabilities. Effort was also often made to include local researchers as authors on publications, which increased their credibility and ability to independently compete for grants. However, on short-term trial collaborations, and even one long-term partnership in Ethiopia, this level of local inclusion did not occur. This was because local staff were frequently only given support roles and they were not involved in planning, analysis and write up stages [37 ,40 ,97 ,98]. Material capacity development was variable, but when there was little investment in laboratory capacity, sample analysis was often done abroad, so local capacity to conduct more advanced methods was not developed [97]. Therefore, although they provided useful early trial experiences and some material gain, their long term impact on research system development was limited. Furthermore, regardless of the collaborative model, most foreign collaborations were largely detached from local institutions and developed their own parallel structures [5 ,35] which reduced the possibility of institutional awareness of trials

and prevented financial, material, and administration capacity development [40 ,46 ,108]. Additionally, almost all material capacity development was thematically focussed, which reduced the ability of local investigators to address broader research topics [10 ,17 ,52].

This all suggests that foreign collaborations can be very effective at developing locally-led trial capacity, but only if they are dedicated to achieving this goal. These findings echo those from the literature synthesis but provide a clearer picture of what dedicated capacity development should look like. However, given the effort and investment required to do this, many international research groups would understandably be reticent to embark on dedicated capacity development. Indeed, one participant in Cameroon suggested that local researchers missed out on collaboration opportunities because conducting research in Cameroon would require too much investment in capacity building. It is likely that to encourage dedicated capacity development, international research actors would need more support, incentives and recognition for doing this. However, this is only the case if macro and institutional-level deficiencies continue. If local bodies invested more in research the level of capacity development effort would be lessened and foreign collaborations may be more willing to try to embed in local institutions and involve local researchers. Therefore, overall, the responsibility for foreign derived capacity development can be argued to lie with both foreign groups and local institutions.

However, even if all foreign collaborations adopted dedicated capacity development, the low number of these trials reportedly did not allow the accumulation of a sufficiently large body of evidence to make wide reaching policy changes, and could not satisfy all the evidence needs of the countries. Furthermore, their sustainability is in question [12 ,22], so although potentially useful, they are not

a complete solution. Based on the above findings and in accordance with newer opinions in HRCD, it appears that locally-led trials have potential to meet national research and capacity development needs and be a more sustainable solution [1 ,14 ,16 ,47 ,48 ,102].

However, currently the potential for locally-led and foreign-led trials to provide useful research and capacity development outputs is being inhibited by macro and institutional-level bodies failing to provide sufficient strategy, support and investment. Consideration of how this situation can be addressed is presented in the following section (7.3.7).

7.3.7 Delivering system-wide prioritisation of health research

There was wide agreement in all the case-studies that macro and institutional level changes are required to support the conduct of locally-led research and clinical trials. This is because although exceptional individuals and institutions are able to conduct trials within the current constraints, most cannot. In Cameroon and Ethiopia where this situation was more severe, even when individuals did manage to lead trials this was often not sustainable. Furthermore, in all case-countries, macro and institutional-level deficiencies reduced the usefulness and capacity development potential of trial research, which lowered the credibility of local trials and the ability to advocate for greater research investment.

Participants in all case-studies suggested a number of macro and institutional-level changes required to enable clinical trial conduct and develop locally-led trial capacity. Increasing investment for local research is essential because lack of finances was the root cause of most system inadequacies in Ethiopia and Cameroon [171][35 ,45 ,111]. Although not yet ideal, the positive effects of even modest investment in research could be seen in Sri Lanka. Indeed, almost all

locally-led trials were enabled by small local grants. Participants in Cameroon and Ethiopia also suggested that small scale pilot grants would be very useful for stimulating locally-led trials, so their potential to support more self-sufficient research appears plausible. Furthermore, based on their availability in Sri Lanka it is likely that such grants would be within the fiscal constraints of many LAMICs. However, in all case-studies it was clear that research grants need to be more demand-driven and strategically provided otherwise research outputs will continue to be fragmented and have limited usefulness for policy. Clearer research strategies would also help ensure foreign collaborative research is aligned with local needs [10 ,17].

In all case-studies, regulatory and ethical bodies lacked sufficient capacity to govern research [41 ,161]. In Sri Lanka this was a key bottleneck to further expansion of R&D. Efforts to develop capacity were present in all countries but these were driven by interested researchers or individual poorly resourced government departments and most regulatory procedures lacked legal backing [155]. To resolve this, greater government attention and investment is needed [26 ,62 ,75 ,160].

To increase the pool of human resources with the awareness, knowledge, technical skills and leadership capabilities to run trials, institutions need to provide greater exposure to research in education [105 ,119 ,157] and daily practice [10 ,28 ,48], and offer more trial work opportunities [10 ,72 ,87]. To provide these learning experiences, there needs to be greater provision of resources and staff with clinical trial expertise to teach research [26], creation of practical learning opportunities [10 ,31], provision of mentorship and knowledge sharing [36 ,98 ,119] and inculcation of pro-research cultures [104 ,122 ,198]. Provision of internationally supplied

learning resources was an important substitute for this, but that HINARI was commonly reported as unavailable and intermittent suggests that a review of accessibility is advisable.

However, the extant pool of researchers with these skills were often not motivated to conduct research and clinical trials [170], so institutions had difficulty recruiting and encouraging staff to do so [26 ,73 ,113]. To increase motivation, institutions need to provide allocated time for research [125], financial incentives [26 ,125], research linked to career progression [119 ,197], and ensure this leads to comparatively better working conditions [83 ,195]. That Cameroon and Sri Lankan governments had recently started offering financial incentives for academics and clinicians shows that such incentives are within LAMIC budgetary constraints.

In Cameroon and Ethiopia, investment in institutional material capacity and infrastructure was desperately needed because capacity constraints reduced the scope of trials [25 ,28] and researchers' motivation and self-efficacy to conduct them [50 ,83 ,176]. Although foreign collaborations sometimes provided resources, these were always thematically focussed, and significant resource constraints discouraged collaborations or led to development of parallel structures. Therefore, it is clear that greater national investment is required [85 ,191]. Although this is likely to be expensive, in Cameroon the government had begun investing in current and new universities. However, mismanagement reportedly wasted some of these investments [62 ,163]. Therefore it appears that such investment is within budgetary constraints of LAMICS, especially if it is judiciously managed.

Governance and administration was seriously problematic in all case-countries due to overly centralised, bureaucratic and hierarchical structures [152 ,153] that did not value or prioritise research [151 ,156 ,157] and were resistant to

improvements [12 ,154]. Such issues are apparently common in many LAMICs and therefore appear largely generalizable [28 ,151]. In addition to making administration difficult, in Ethiopia and Cameroon obstructive procedures made investigators apathetic about conducting research [24 ,72 ,130], and encouraged local and foreign groups to set up parallel structures [40 ,46 ,108]. To resolve these issues, it is clear that there needs to be greater accountability for administrators [35 ,193], procedures need streamlining [55 ,121], dedicated research services need to be provided [28 ,47 ,155], and promotion of decision-makers should be more meritocratic [193] and based on research experience [157]. However, in addition to overhauling administration structures, researchers and funders need to value and invest in administration [48 ,55], provide overheads [26], and engage with administrators more closely [32 ,73 ,155] if research services are to work more efficiently.

In all case-studies, policies bodies require further investment and capacity development to be able to understand, use and demand research [28 ,31 ,151]. However, researchers also need to conduct more applied and targeted research to make evidence useful for policy [108 ,111]. This could partly be resolved by developing research strategy and providing better support and resources, but it also appeared that researchers need incentives to make research useful. This was evident in both Sri Lanka and Cameroon because although research incentives had increased trial conduct, investigators only valuing research as a means to qualifications or salary top-ups meant much of it was not useful. Therefore, to encourage more impactful research, research quality and policy impact should be part of assessment criteria for continuation of research incentives. Researchers also need training in research dissemination to facilitate policy uptake [10 ,28 ,48 ,115].

Although the aforementioned improvements are important for facilitating locally-led research and trials, if the research systems in all case-countries remain fragmented the increased capacities are unlikely to be harnessed. This appears true for many LAMICS [4 ,10 ,24 ,30]. To leverage capacity investments, all research actors and stakeholders need to work together towards common goals. Based on the previous sections, the key to this appears to be personal, regular and active engagement.

To achieve this, networking platforms that allow actors and stakeholders to personally communicate may be helpful [7 ,28 ,181]. These could be online [62 ,184] or in person [7 ,185]. Support for this comes from the HRCD literature that suggests networking builds trust and understanding between stakeholders [133], encourages knowledge sharing [24], helps resolve leadership disputes, and encourages cooperative working towards common goals because there is less centralised leadership [67 ,131]. As such, increasing networking may also help break up divisive professional groupings. Indeed reports from participants in Cameroon and Sri Lanka support this because they said working on clinical trials together with diverse stakeholders improved professional relations. This suggests that providing the aforementioned pilot grants contingent on local collaboration may help improve professional relations as well as the quality and scope of trials.

However, most successful examples of networking involve international or regional networks [17 ,105 ,132 ,137], which while being globally helpful, still fail to create national connections [133]. One exception is The Global Health Network [212] networking facility which has resulted in the formation of several country level networks between research actors and stakeholders who were previously unknown

to each other. Together they organise in-country networking and training events that are reportedly very effective at increasing capacity and developing local relationships. Examples from Central and West Africa appear particularly sustainable [to be published]. This strongly suggests that online networking can promote improved research relationships. However, it is important to note that in the example above, online networking was supplemented with in-person networking during workshops. As such, it is not clear if online-networking alone, without personal contact follow-up, could create such productive relationships.

As shown by the citations above, most of these macro and institutional level deficiencies, their consequences and need to be addressed are widely recognised in the HRCD literature and thus this situation appears to be largely generalizable to many LAMICs and also health research in general. Furthermore, based on the above findings, many of these changes do appear to be within budgetary constraints of LAMIC countries. Although not mentioned by participants, the HRCD literature makes a number of suggestions for innovative funding mechanisms [45 ,177 ,187 ,188] that may help national governments raise revenue for research.

To get national governments to implement these changes, reports from both Cameroon and Sri Lanka and authors in the literature suggest that advocacy from research leaders are important for driving these changes [22 ,23 ,34 ,80 ,121]. This is because research leaders can potentially encourage top-level decision-makers to value clinical trials and research, and thus see them as a good investment. To do this, clinical trials need to be useful for healthcare policy [47 ,85], but reports from Sri Lanka and Cameroon also suggest that capacity development benefits are important in these advocacy negotiations. This argument is novel within the HRCD

literature, but is supported by the observation that in Sri Lanka the treasury department decided to encourage clinical trials based on their economic and development benefits. Thus a plurality of advocacy strategies, tailored to what different stakeholders' value is likely to be necessary.

Viewing local researchers as active agents of system changes is an exciting prospect which is supported by issue selling theory [267]. However, to be able to conduct more beneficial trials and advocate for resources, research systems need strengthening and institutional hierarchies need to support, not hinder, these bottom-up initiatives. If this is not done, the conduct of quality health research is likely to be unsustainable because researchers may give up trying or move outside the local research system in search of better working conditions. This appears to lead to an impossible situation where top-level decision-makers are unwilling to take the lead in initiating a virtuous cycle of research system investment and research leader support without experiencing gains from clinical trials [8 ,99 ,152], but this is hard to achieve without first receiving investment.

However, some clinical trials that do provide health and capacity development benefits are already being conducted by exceptional local investigators in the face of these challenging environments. If these individuals could become clinical trial “champions” they may be able to sway the balance [27 ,202] by building a movement towards valuing evidence-based medicine, and thereby getting macro-level actors to begin supporting and investing in research and clinical trials. Furthermore, international collaborative trials can contribute to this because they can support excellent research evidence generation and capacity development, as long as they are dedicated to both these outcomes. Even if subsequent investment is modest, findings from Sri Lanka suggest that this could stimulate enough locally

beneficial trials for top-level decision-makers to recognise their importance and take over capacity development responsibilities. However, it is important that local researchers and foreign collaborators put effort into creating a sustainable, more self-sufficient national research system, or it may be left in a state of limbo where governments fail to take on responsibility and local researchers continue to be dependent on foreign partners to plug the gaps [22 ,23 ,35 ,105].

7.3.8 Limitations of the framework

It is important to note that while the conceptual framework for the antecedents and consequences of locally-led trial undertaking provides detailed and robust arguments informed by primary evidence, the HRCD literature and relevant wider theories, it is unlikely that it completely explains all the drivers and inhibitors of locally-led trial conduct, even within the investigated countries, as these will inevitably vary to some degree with space and time. Although unknown variations in research system capacity may contribute to some context specific differences, the exhaustive comparison with the literature suggests that most mechanisms caused by capacity issues have been identified.

Rather the main variations from the mechanisms described are likely to be caused by individual differences. This is because locally-led trial undertaking is driven by individual decisions, capabilities and effort; and while these factors can be predicted to some extent based on other individuals' experiences and psychological and organisational theory, some individuals are likely to react differently to common stimuli. Indeed it is for this reason that established models explaining workplace behaviours often include innate personality components as variables within their models [248 ,272 ,273]. This could be most clearly seen in the findings where some individuals were able to successfully lead trials with little or no

previous experience. Also that some individuals were sufficiently motivated to lead trials solely based on intrinsic incentives shows how a minority of individuals can differ from the majority. It is also likely that personal experiences outside of those reported in the workplace could strongly influence an individual's attitudes and behaviour. For instance success in other areas of an individual's life may boost their confidence in work tasks. However, because this study did not collect this information, such drivers were hidden. Equally national or group cultures not considered in this analysis are likely to be important. For instance, psychological conservatism, norm-breaking behaviour, and attitude to risk taking would all be relevant to the conduct of locally-led trials, and all are known to vary according to national cultures [279].

However, the goal of this framework was to identify the key practical issues influencing locally-led trial conduct for the majority of people. Based on the data saturation within case-studies, similarities between case-studies, congruence with established organisational and psychological theory, and identification of most if not all issues reported in the literature, this appears to have been achieved.

7.4 Recommendations to develop sustainable locally-led trial capacity

The aim of this thesis was to produce reliable and robust evidence-based recommendations for the facilitation of locally-led clinical trials in Low and Middle Income Countries. The conceptual framework describing the antecedents and consequences to locally-led trial undertaking provides a firm empirical and theoretical basis on which to form these practical recommendations. Although other literature has been used to develop understandings of the findings and suggest transferability and generalizability, recommendations will not be made based on literature alone. This is because this thesis aimed to produce recommendations

based on contextually situated empirical findings, rather than repeating one-size-fits-all models [24]. By presenting these recommendations alongside the conceptual framework, further details on the evidence context, degree of transferability, and theories of change informing the recommendations are clear.

Understanding of the key enablers leading to locally-led trial capacity development and the theories of change driving these changes led to the identification of four key inter-related goals for promoting locally-led trial conduct in LAMICS: *fostering pro-research cultures in stakeholder institutions; developing trial leaders and staff; providing a facilitative operational environment for trials; and ensuring trial research has an impact*. These goals, and the mechanisms by which they can promote locally-led trial conduct, were identified by grouping the lower-level theory developed in the conceptual framework (antecedents and consequences of local trial undertaking, page 309) into categories of higher-level mechanisms that may ultimately lead to the desired outcome of increasing locally-led trial conduct in LAMICS. These goals encompass and connect all the enablers in the conceptual framework into a long-term action-orientated strategy for capacity development that is self-reinforcing and therefore more likely to be sustainable.

The recommendations for *fostering pro-research cultures* focus on generating top-level buy in for trials to secure investment, generate support and appreciation for trial research and increase the pool of potential researchers willing and confident enough to conduct trials. Recommendations for *developing trial leaders and staff* concentrate on resolving skills gaps of academics and healthcare staff so that they can undertake trials, and developing future research leaders that have the capabilities to successfully manage trials in challenging environments, support the development of local staff and institutions, and can act as champions for greater

research investment. Recommendations for *providing a facilitative operational environment for trials* aim to reduce operational barriers to trial conduct and increase the finances and material resources available to future clinical trials so that they can be conducted with greater scope, quality and ease, therefore making the conduct of clinical trials within local institutions more of attractive prospect for local and international researchers. Recommendations for *ensuring trial research has an impact* not only aim to make clinical trial evidence useful for policy and have an impact on population health, but also demonstrate that local trial research is credible, valuable and offers a good return on investment so that pro-research attitudes and support for trial research is reinforced.

The table of recommendations to develop locally-led trial capacity in LAMICs is shown in figure 7.2. The “Goal” column shows the categories of higher-level mechanisms for achieving the ultimate outcome of increasing locally-led trial conduct in LAMICS; the “Logic for change” columns details the mechanisms by which the Goals may increase locally-led trial conduct; the “Strategy”, “Implementation” and “Theory of change” columns show the lower-level activities and mechanisms that should lead to the higher-level goals and mechanisms; the “Agent of change” column details the parties with the ability to implement the mechanisms; and the “Context” column details the contexts where the mechanisms are likely to be more important.

Table 7-2 Recommendations to develop sustainable locally-led trial capacity in LAMICs

Goal	Logic for change	Strategy	Implementation	Theory of change	Agent of change	Contextual relevance
Foster pro-research cultures in stakeholder institutions	Encourages top-level investment & prioritisation of trials Encourages institutional staff & decision-makers to support not hinder trials Increases pool of researchers willing & confident enough to conduct trials, & reduces brain-drain	Explain trial & research methods & potential benefits for patients, institutions & individuals	• Research & trial exposure in education & workplaces • Engage & inspire through mentorship • Access to training & knowledge resources • Organise seminars, workshops	Increases awareness & desire to conduct trials, & top-level buy-in & support for trials	• Institutional level • Research leaders • International actors	Where negative research cultures or lack of interest in trials impedes operations & prevents investment
		Provide opportunities for institutional staff to see trials conducted & practically get involved	• Conduct trials in institutions & involve local staff • Allow wider participation through exchange placements • Seeing successful simple locally-led trials most effective	Increases awareness & desire to conduct trials Increases motivation & self-efficacy by reducing perception that trials are difficult	• Research leaders	
		Provide intrinsic & extrinsic incentives for employees to conduct or get involved in trials	• Financial rewards & salaried time for research • Research linked to career progression leading to better working conditions • Make rewards accountable & contingent on continued performance, especially in academia • Appreciation & applauding research	Increases motivation to conduct trials	• Macro & institutional level • Research leaders • Colleagues	Where skilled or junior staff show little inclination towards trial undertaking
		<i>Provide facilitative operational environment for trials</i>	<i>See following section in recommendation table</i>	Increases motivation & self-efficacy to conduct trials by making trials more achievable	<i>See following section in recommendation table</i>	Where brain-drain problematic

Develop trial leaders & staff	Human resources for research are essential for increasing trial conduct, either locally or foreign-led	Provide basic & advanced skills training & refresher courses	• Increase research components in educational curricula • Provide continuing education in workplaces • Skills courses & workshops • E-learning & distance learning • Fellowships & advanced degrees • Use train-the-trainer models • Use more applied teaching techniques	Improves knowledge, develops technical skills, reinforces motivation, & increase self-efficacy	• Macro & institutional level • Research leaders • International actors	Where extant expertise is insufficient, to meet demand
	Resolving key skills gaps essential for researchers to gain funding & conduct trials	Focus on clinical trials & key skills gaps. Ensure regular & sustainable. Best if locally applicable				
	Healthcare & ministerial staff need comprehensive research skills, as well as academics	Provide practical research experiences on trials	• <i>Provide facilitative environment to encourage complete conduct of trials in institutions</i> • Offer full involvement, responsibility & challenging work to local staff • Value staff contributions, share benefits & recognition • Provide mentorship & comprehensive training	Most effective technique for mastering technical skills & developing leadership capabilities; self-efficacy, issue selling, team leadership	• Research leaders • Foreign-collaborators	Where staff have key skills gaps that prevent of impede trials
	Development of research leaders is essential for locally-led trial conduct	Locally-led trials & long-term foreign partnerships usually best	• Organise seminars & workshops • Encourage teamwork cultures & on-the-job knowledge sharing by developing leadership capabilities • Organise mentoring relationships • Use international networks if unavailable locally	Increases team working & motivation		Where there are insufficient research leaders
	Research leaders needed to foster pro-research cultures, encourage teamwork, provide training & mentorship, develop new research leaders, & advocate for greater investment	Provide knowledge sharing & mentorship opportunities	• Provide libraries, computers & reliable internet • Supply open access journals • Ensure access to HINARI • Supply e-learning • Supply online or offline research guidance resources	Shares tacit knowledge & provides support which increases knowledge, technical skills, motivation & self-efficacy	• Institutional level • Research leaders • Colleagues • International actors	Where research leaders lack leadership capabilities – often present in centralised & hierarchical work environments
		Provide open, easy access to knowledge resources		Supports independent learning which increases knowledge & motivation	• Macro & institutional level • International actors	
		Best if locally applicable				

Provide facilitative operational environment for research	Reduces barriers to trial conduct which increases self-efficacy and motivation to undertake locally-led trials	Provide funding for clinical trials	• Offer more grants available for LAMIC researchers & disease priorities • National research grants ensure local researchers can obtain them • Pilot grants for early researchers to gain experience & build portfolios • Grants exclusively for trials can boost trial conduct	Even modest grants can enable simple but important locally-led trials	• Macro-level • International actors	Where trial are prevented or impeded due to operational barriers or material resource constraints
		Must be sufficient to allow research of useful scope		Improves chances of gaining more competitive funding		
	Encourages international partnerships	Improve research governance & administration procedures & increase capacity to support research	• Promote decision-makers based on research experience • Streamline procedures for minor requests • Update regulations & introduce accountability • Trials use institutional research services • Early engagement between administrators & researchers • Budget research services into grants	Speeds up trial operations & frees investigator's time	• Institutional level • Research leaders	Where operational barriers or material resources reduce the quality & scope of trials
	Encourages local & foreign-led research to be conducted through local institutions	Strengthen regulatory & ethical review capacity & procedures	• Provide funding & training for review boards • Ethics training for investigators • Build monitoring capacity • Develop legal framework & government backing for regulatory bodies	Ensures trials are safe & ethical, allows more ethically complex trials, speeds up trial operations	• Macro & institutional level • Research leaders	
	Allows local researchers to negotiate for more beneficial partnerships	Develop material resources & infrastructure	• Provide sufficient building space with reliable water & power • Provide required advanced & basic laboratory equipment & supplies/maintenance • Provide sufficient ICT access with reliable internet	Facilitates operations & enables trials with greater scope & quality	• Macro & institutional level	
	Facilitates trials of greater scope & quality & increases capacity development	Support local collaborations among research producers & stakeholders, & encourage team working	• Develop networking platforms to identify & bring together all local stakeholders • Make some grants contingent on local collaboration • Fair incentives & benefits for all research actors • Develop & use research leader skills to improve communication, relationships & team working	Leverages resources to reach a critical mass capable of self-sufficiently undertaking trials. Improves trial operations.	• Macro & institutional • Research leaders	
	benefits which supports advocacy for greater investments	Encourage valuable foreign partnerships	• Provide international networking platforms • Ensure foreign-collaborations have sufficient capacity to work within local institutions, without major investment • Negotiate partnerships that have strong local leadership, share benefits fairly, are dedicated to capacity development, & ideally conduct trials in local institutions	Enables more resource-intensive research & helps develop local capacities	• Macro-level • Research leaders • International actors • Foreign-collaborators	Where operational barriers or material resources prevent beneficial collaborations or capacity development
	Long-term partnerships most useful					

Ensure research is useful and has an impact	Trials must influence policy and have an impact on health outcomes for them to be considered valuable Useful & impactful trials develop & reinforces pro-research attitudes by showing benefits & returns on investments Increases credibility of locally-led trials which is needed for research leaders to advocate for further investment	Develop & implement clear research strategy to focus investments around research priorities	• Identify research priorities • Develop & disseminate clear research strategy • Focus local grant funding on key areas & make grants demand-led • Focus institutional investments on local departments & resources required to meet research goals	Ensures most efficient use of resources & builds an evidence base capable of informing policy changes	• Macro-level	Where trial evidence has limited use for policy or is not effectively disseminated Where research users lack capacity to translate research & implement policies Where poor communication & engagement impedes translation of evidence into policy
		Develop policy-makers interest & capacity to demand & utilise research, & implement policies	• <i>Foster pro-research cultures & attitudes</i> • Provide training for policy makers to demand & utilise research • Ensure resources available for policy implementation	Ensures research has an impact & improves patient care	• Macro-level	
		Develop research producers interest & capacity to respond to research strategy, produce useful outputs & disseminate findings effectively	• Research grants, incentives & rewards dependent on quality & impact • <i>Provide a facilitative operational environment conducive to useful research</i> • <i>Develop research leaders</i> who can effectively interact with these bodies • Provide training on research dissemination for publication & policy • Ensure time & resources available for disseminating findings • Research leaders need to be dedicated to impact	Ensures research findings will be useful for policy & are effectively disseminated to influence policy	• Macro & institutional level • Research leaders	
		Increase engagement between strategists, producers, & users of research	• Develop networking platforms to facilitate interaction between these stakeholders • Engage early & regularly • Dedicated liaisons may be helpful	Builds communication & trust between knowledge cycle actors which facilitates translation of research	• Macro-level • Research leaders	

The table of recommendations shows the multitude and diversity of strategies that can be employed to achieve the four main goals. Importantly, some implementation strategies can help achieve several goals. For instance, conducting trials in institutions can help facilitate pro-research environments, develop research leaders and staff, and build capacity for a facilitative operational environment. Therefore, if resources for development are limited, selecting strategies that can have multiple positive effects may be the first actions to take.

The recommendations also emphasise that a multitude of agents are responsible for changes, not just macro-level decision-makers. This clearly supports arguments that the whole research system needs to work together towards common goals to ensure positive outcomes. Research leaders have a particularly strong role to play, despite their lower positions in the hierarchy of decision-makers. As such, supporting the development of research leaders, not just research staff, is extremely important to locally-led trial capacity development.

However, it is important to note that when institutional structure is resistant to bottom up change or research systems limit investigators' ability to undertake quality research, research leaders often become despondent. This may result in them either giving up attempting to conduct research or moving outside the local research system to achieve their goals. Therefore it will be important that the recommendations for fostering pro-research cultures, providing a facilitative operational environment for research, and ensuring research is useful and has an impact are implemented alongside the recommendations for developing research leaders and staff. As presented in section 7.3.8 (delivering system wide prioritisation of health research, page 341), such simultaneous improvements may be difficult to initiate without first demonstrating the benefits of good quality research. Therefore

the existing cadre of research champions who continue to undertake quality research in the face of challenges are likely to be very important for providing the initial push for these recommendations to be implemented.

Although the recommendations did not address supra-national development issues, international development & research actors are named as agents of change where participants said they could contribute to research system development.

As stated previously, the individual findings in this thesis have many similarities to those described in the HRCd literature. The conceptual framework and recommendations for developing sustainable locally-led trial capacity also have key similarities to the main guides for health research capacity development [45 ,47 ,115 ,122] recognised in the 2013 World Health Report [1]. Although there are many minor similarities (these are covered in table 7.1), the main conceptual and high-level similarities include: taking a system-wide approach to capacity development; focusing on training individuals and research leaders to conduct research, especially using learning by doing approaches; developing institutions to provide a research environment conducive to encouraging and supporting research; encouraging collaborations and partnerships to help develop capacity and enable research where institutional capacity is not yet sufficient; addressing macro-level deficiencies in stewardship, regulation and governance; and encouraging financing of research, particularly through advocacy. Given that these development guides relate to general health research capacity, not clinical trials, this strongly suggests that the conceptual framework and recommendations for developing locally-led trial

capacity produced in this thesis will also be useful for developing other types of locally-led health research capacity in LAMICs.

In addition to including and strongly building upon the more commonly accepted components of research development, the recommendations in this thesis also identify several novel but very important factors to locally-led trial capacity development. These include the need for research exposure and advocacy to emphasise capacity and financial development benefits of clinical trials, as well as health benefits; the importance of non-monetary and career incentives for increasing motivation to undertake trials; team working improving trial performance, motivation and learning; the importance of self-efficacy, issue selling, and team leadership as facilitative capabilities to research leadership, and how these capabilities can be developed or inhibited; the importance of responsibility and challenging work for increasing motivation and leadership capability development; that locally-led trials can offer the best experiences to develop these leadership capabilities and motivation to undertake trials; and how to improve professional relationships. While some of these novel elements require further investigation to clarify the concepts and confirm generalizability, all appear highly plausible and very likely to be relevant to broad LAMIC research contexts.

However, it is important to note that while the recommendations are broadly useful, not all recommendations will be useful for all context or development goals. This is because there is considerable variation in the barriers and enablers to locally-led health research even within research systems. For instance, although self-efficacy was an issue in healthcare settings in Sri Lanka, it was not problematic in academia. Therefore there would be little point in implementing strategies to

increase self-efficacy in academic institutions. As such, before implementing recommendations, a good understanding of the intended development context is needed. This is so it can be understood if a recommendations' goal, change logic, theories of change, and context-specificity will be relevant and appropriate for the intended development context. If this knowledge is not known, conducting a situational analysis would be advisable [24 ,52]. In the words of ESSENCE on Health Research, capacity strengthening is “more than just providing training or distributing manuals; it is a complex process that involves shifts in power, provokes changes in systems and is influenced by factors such as cultural values. These factors all have to be considered when designing capacity strengthening interventions” [48].

However, that the recommendations in this thesis present the possibility of assessing which recommendations might be useful for a specific development context is very important for their practical usefulness. Furthermore this appears novel within the HRCD literature. This is because none of the previously mentioned capacity development guides supplied any indication of where the evidence for their recommendations came from, they were all highly generic with no reference to the contexts their recommendations would be useful for, little detail is given on how their recommendations can be implemented, and there is no consideration of theories of change behind the recommendations [28 ,30 ,31 ,47 ,53 ,121]. Therefore it would be very difficult to inform the design of a development intervention based on these recommendations. Furthermore most other literature support for these recommendations is not empirical, and those that are only focus on broad academic development [26 ,220], did not use prospective research designs [14 ,30], do not provide clear reproducible methods [12 ,31 ,37], or only focus on one-country [110

,155 ,220] or international research partnerships [16 ,121 ,196 ,209]. Therefore, to my knowledge these recommendations are the most robust and practically useful guidance for the development of locally-led trial capacity in LAMICs.

One example where many of this thesis's recommendations already appear to be being successfully implemented is that of Tanzania. The National Institute of Medical Research in Tanzania was set up in 1979 and has progressively evolved into the coordinating mechanism for the National Health Research System. This system now has a flourishing research environment consisting of a number of excellent research institutions that support the training of a large number of specialist research staff that conduct a broad range of locally-relevant health research. All this has been achieved despite the research system suffering from common deficiencies: inadequate national funding and a reliance on foreign support, inadequate human and material resources, and poor research uptake. Although not completely resolved, there appears to be a real prospect that these deficiencies will largely be addressed by 2019 and Tanzania will be able to meet its current and future research needs [280].

This success appears to be due to following a clear research vision articulated through successive strategic plans. The most recent strategic plan covering the years 2014-2019 proposes very similar actions to those advised in this thesis. These include: developing clear research priorities and investing in these areas [281]; improving research governance and support structures to increase the performance of institutions; developing administration and research support systems; investing in material resources and infrastructure; conducting a review of human resource management and offering greater training, career development and incentives to

encourage research conduct and leadership; strengthening regulatory and ethical review and monitoring capacity; improving utilisation of research findings through better dissemination and policy dialogue, and developing knowledge sharing forums and knowledge management systems; and increasing advocacy of research benefits by sensitising and engaging with decision-makers [280].

The similarities of this thesis's recommendations to the strategic plan of this arguably progressive and historically successful research coordinating body, suggests that the recommendations proposed in this thesis will have real-world value and are likely to be practically useful for health research development.

7.5 Overall strengths, limitations and further work

The strengths and limitations of this thesis have been addressed throughout the individual chapters. This section will provide a concluding summary on the strengths and weaknesses and consider areas for further investigation.

Overall, this thesis was successful in answering the research question and achieving its aims and objectives. The chapter 2 literature syntheses gave a detailed yet broad overview of the barriers and enablers to health research in LAMICS. Importantly it demonstrated how little solid evidence there was guiding health research capacity development and in particular the acute knowledge gap on the best ways to support locally-led trial conduct. This not only provided additional support for the importance of the research question, but also helped inform the research design, analysis, interpretations, format of the final development framework and recommendations, and establish the wider generalizability of the findings and recommendations to other research contexts and types of health research. Identification of the failures of many development strategies to effectively develop sustainable more self-sufficient LAMIC research capacity was very

revealing. It also led to the argument that dedicated capacity development, where development gains are valued equally or more than research outputs, is needed in situations where capacity development is an explicit goal. Indeed, this literature synthesis is probably the most complete and detailed literature review on health research capacity development in LAMICs published.

The three case-studies in Ethiopia, Cameroon and Sri Lanka produced a thorough and nuanced account of the key barriers and enablers to locally-led trial conduct in LAMICs. They also demonstrated that LAMIC research actors consider locally-led trials to be important and that locally-led trials can produce useful research outputs and are in themselves a useful development tool. Given the findings congruence with country-specific and general literature on health research systems in LAMICs, these findings appear highly plausible and robust.

These empirical findings on locally-led trials are a first within the HRCD literature, and as such, are completely novel. However, due to their wider applicability to other types of health research, they also provide strong empirical support for general health research developing thinking (something which was previously lacking), add significant detail to current knowledge, and contribute novel findings. Although some of the novel findings require further research, the strong incorporation of organisational change and psychological theory helped develop an understanding of the issues and suggested that they are highly plausible and likely important in other settings. The findings were particularly strong in developing an understanding of the individual-level issues determining locally-led trial undertaking. Since these issues are regarded as the most important influences on local research leadership [1,115,221], these findings are likely to be very useful.

The qualitative case-study design used in this thesis was critical in eliciting these in-depth findings. This design followed many established good research practices for qualitative research and case-studies in order to ensure high quality and robust findings [218 ,223 ,236 ,282] and was clearly ethically sound and sufficiently participatory given the large number of regulatory, ethical and administrative approvals it received. More detailed consideration of the limitations of the study design and how these were justified and minimised is presented in section 3.12 (page 113). The use of a pilot study was helpful in allaying study design concerns because it showed early on in the study that although there were limitations, the methods were still capable of producing high quality and robust data.

The recruitment methods were successful in eliciting highly useful and diverse reports on the barriers and enablers to locally-led trial conduct throughout the research system. Furthermore, the findings were made more interesting and valuable because they drew on the perspectives of local actors and stakeholders, and therefore presented an alternative, much needed bottom-up view [24] on health research capacity development. As such, this thesis goes some way to answering calls for greater local stakeholder inclusion in development decision-making [10 ,79].

All the research methods were highly successful, well received by participants, and were able to contribute different kinds of data. Furthermore, the use of process mapping exercises as a qualitative research tool appears novel, since none of the papers in HRCD literature did this, and I am unaware of its use in this way in any other formal medical research. Indeed the method adopted was entirely of my own design, only being informed by its use in the NHS to understand patient pathways and possibilities for operational improvement of services. As such, the development

of this research method and confirmation that qualitative process mapping is a useful research tool is an important side-outcome of this thesis.

The thematic analysis and generative causation approach used in Realist research methods [218] was very helpful for analysing and interpreting the findings, particularly identifying the mechanisms that drove and connected issues within the research system. Taking a systems approach and using conceptual models to present these findings also helped to clearly show how the mechanisms operate. Indeed, this approach identified several novel theories of change and was very important for establishing transferability and generalizability of findings, in addition to the literature synthesis. This is because it showed that although the barriers and enablers may vary by research context, the importance of the research system components and the mechanisms by which they exert influence remained similar in all contexts.

Establishing how the case-study findings were generalizable permitted the development of the final conceptual framework and recommendations for developing locally-led trial capacity in LAMICs. These not only contribute a great deal to the literature because they are entirely novel for their specific application to locally-led trials, but also because they greatly add to existing recommendations designed for general health research capacity development. Indeed the final conceptual framework and recommendations go way beyond other recommendations to develop LAMIC research capacity because they are empirically backed, contain novel arguments, and pay close and detailed attention to how and why specific recommendations will work and in what circumstances, and they also consider long-term sustainability.

These novel elements of the recommendations are very important because they allow potential development actors to understand which recommendations will be most useful for their intended context. As such, the conceptual framework and recommendation's in this thesis are perhaps the most practically useful general guidance for developing locally-led health research capacity published in the literature. The provision of this guidance is also very timely. The 2013 World Health Report [1] confirms the continuing importance of the research question and need for locally-led health research, and provided a useful recent and influential document around which to frame the results. Indeed, this study answers the need for more guidance on health research capacity development in order to fulfil the goal of the 2013 World Health Report - "All nations should be producers and users of research as well as consumers" [1].

Nevertheless, this thesis and the findings were not without limitations. Foremost, is that only three case-studies were conducted, and two of these were in similar research contexts. That the three case-studies captured most if not all the issues reported in the HRCD literature suggests that the findings do account for the vast majority of issues. However, that this study identified several novel factors through only three case-studies also indicates that other important issues may as yet be unidentified. This is likely to be especially true in dissimilar research contexts to the cases investigated. Therefore, further research in more and diverse research settings is needed to ensure that the whole array of issues impacting on locally-led trials in LAMICs are identified.

The findings and conceptual framework presented in this thesis will be a very useful starting point for this expanded research. Indeed, I have already initiated a

research collaboration in Peru so that a local research group can repeat this study in Latin America in order to understand if the conceptual framework and recommendations are relevant there, or if other issues and mechanisms are also important. Another option being considered by The Global Health Network is to design a global quantitative survey for use in developing countries to understand the extent of barriers and enablers to trial conduct in different settings. This survey would be based on the findings of this thesis.

However, it is also possible that the findings do not capture all the issues even within the case-studies. This is suggested by the fact that several issues shown to be important in Cameroon and Sri Lanka were not identified by participants in Ethiopia, but were shown to be important in Ethiopia by other literature e.g. centralised hierarchies and team working impacting on research. The most likely reason for this is that data saturation was not reached in Ethiopia due to its pilot nature, but it is also possible that the less refined questioning in the Ethiopian pilot failed to illicit details on these factors. This suggests that participants may not themselves identify all the issues important within their research system, and that their responses are limited by the questions asked. Therefore some issues may have gone unidentified because the topic guides did not successfully solicit illuminating answers.

However, that several unexpected factors were identified suggests that the open, semi-structured, and sometimes free narrative style of questioning was successful at eliciting broader issues beyond those originally considered when designing the topic guides (see appendix for the initial topic guides used in the Ethiopian case study and the final topic guides used in the Sri Lankan case-study, page XVI). Furthermore, the main objective of this thesis was to identify the high-

level key issues that most severely impacted on locally-led trial undertaking, which has been achieved. Therefore even if some subtle nuances were missed, this would not have meaningfully changed the final findings.

However, concentrating on discovering the broad array of high-level key issues influencing locally-led trial undertaking came at the expense of missing out on more in-depth analysis of specific influences on trial undertaking. As such, although this thesis raised a number of novel issues and potentially important contributions from organisational and psychological theory, these could only be explored to a limited degree. This was a necessary trade-off because before this thesis so little was known about the influences on locally-led trial conduct that it was not known which issues should be concentrated upon. Furthermore, only after the combined analysis of all three case-studies was it clear which factors should be prioritised for further investigation.

It is also true that the recommendations do not provide specific suggestions for overcoming complex macro-level issues such as funding strategies and regulatory frameworks. However, there are already some detailed contributions discussing these issues in the HRCD literature [45 ,177 ,188] [283-286] that are likely to be relevant to locally-led trials. Nonetheless, further research that more deeply explores specific issues influencing locally-led trial undertaking is warranted. Indeed, in the final year of my DPhil, I supported and guided an MPhil student on her thesis which was designed to assess the impact of networking meetings and platforms for encouraging locally-led health research in Zambia.

The exclusive focus on recruiting LAMIC participants also represents another compromise in the research design. While this ensured a bottom-up LAMIC country view on health research capacity development, it meant that international

researchers and development actors were not given the opportunity to offer their perspectives. As such, when interpreting the results, the contributions of local participants had to be taken at face value, without seeking corroborating, contradictory, or justifying arguments from international actors. Therefore this thesis was biased in the views it presented. However, the chapter 2 literature synthesis explored in detail all of the international and LAMIC narratives on health research capacity development and it was clear that most of the arguments presented by participants in this study were fairly representative of current thinking and therefore seemed generally accurate and fair.

A final important point about this thesis's methods and the findings is that they were based on qualitative opinions and participant recall of events, so some recall bias may have been present and there was inherent subjectivity within participant opinions. Furthermore, it was not possible to put a quantitative value on the effects that barriers and enablers had on trial conduct. In response to these limitations, I have worked with The Global Health Network to design a real-time evaluation of a clinical trial being implemented in Ethiopia. This study includes the collection of real-time qualitative and quantitative operational data and includes observational methods. The hope is that this can more objectively link trial issues to causes and give a more quantitative indication of effects on trial undertaking.

7.6 Outputs from this thesis

Two first author publications have already been produced as outcomes of this thesis. These were published in BMJ Open [238] and a special edition of The Lancet [246]. Copies of these articles can be found in the appendix (pages XXXIX and XLIX). I also plan to publish the chapter 2 literature synthesis which will be targeted at PLoS Medicine, and the overall findings including the conceptual framework and

recommendations for developing locally-led trial capacity which will be targeted at The Lancet. The findings have also been presented at numerous conferences, most notably at The World Health Summit in Berlin in the form of a poster and oral presentation in front of UN and European Union leaders. I also plan to produce a policy style document on the findings of this thesis and hope to be able to present this in person to international development actors, including the European and Developing Countries Clinical Trial Partnership.

The findings from this thesis have also greatly contributed towards the continuing development of The Global Health Network, both in terms of future research and service provision. I have contributed to several successful grant applications where the data from this thesis has been used to justify funding. Furthermore, this thesis has been instrumental in the design and development of two novel tools supporting global health research in developing countries; The Process Map, and SiteFinder. An article on SiteFinder, in which I am second author, has been accepted for publication in PLoS NTDs. A draft copy of this can be found in the appendix (page L). An article in Nature Medicine praising The Process Map can also be found in the appendix [278] (page LVII).

7.7 Conclusions

This thesis set out to identify, understand and explore the key barriers and enablers to locally-led clinical trial conduct in Low and Middle Income Countries, and to use this knowledge to develop reliable and robust evidence-based recommendations to facilitate their conduct.

The findings from this thesis show that LAMIC research systems have a multitude of deficiencies that negatively impact on the successful undertaking of locally-led trials. These barriers occur at all levels of the research system and make it difficult for local researchers to accumulate the required skills and resources and overcome operational barriers to successfully conduct clinical trials. Even when this is achieved, failure to provide sufficient resources, strategy and support for local trials means that their outputs are often fragmented, of limited scope, and it can be difficult to influence policy and practice. As a result, local trial research often lacks credibility which makes it hard to advocate for greater investment. This thesis also identified a multitude of enablers to locally-led trial conduct. These are essentially strategies and actions required to cope with current constraints and resolve barriers in the research system so that trials can be more easily and productively conducted.

Although different country research systems, and institutions and individuals within them were variably successful at conducting trials, the key issues and mechanisms influencing successful trial undertaking were largely similar. Congruence with wider literature strongly suggests that the majority of these findings are largely generalizable to Low and Middle Income Countries and are also likely to be relevant to other types of health research.

Overcoming these diverse barriers and delivering enablers to locally-led trial conduct will require multiple, inter-related interventions that seek to resolve them in a holistic and sustainable manner. However, current development strategies all too often adopt short-term or vertically targeted interventions with the main aim of enabling the expedited production of specific research outputs. Although this gets clinical trials done and can produce useful research outputs, sustainable and self-reinforcing capacity to more independently address local research needs is rarely developed.

This thesis concludes that if the World Health Organisation's goal of all nations being producers and users of research [1] is to be achieved, then development activities that are dedicated to developing sustainable capacity to conduct a broad range of locally-led trial and health research are needed. Although this point of view is not novel, this research represents the first empirically-backed findings in support of these arguments. Furthermore, the conceptual framework and recommendations produced are the first evidence-based, and contextually and theoretically detailed guidance to practically help towards achieving this goal.

Critically, the conceptual framework shows that multiple actors have responsibility for implementing these changes, and encouragingly progress towards the development of locally-led clinical trial and health research capacity is being made in LAMICs. However, given that LAMIC governments are generally reticent about investing in health research, the actions of local research leaders with the support

of international partners will be important for demonstrating the value of locally-led trials and building the political will to scale-up investment.

Although this thesis has provided evidence on both recognised and novel issues influencing locally-led trial conduct in LAMICs, key questions still remain. Further research testing the applicability of the theoretical framework in diverse research settings is needed to understand the limits of its generalizability, and if necessary to tailor the recommendations for particular contexts. The novel factors identified in this thesis also present fertile research topics to explore in more detail, now that they have been shown to be relevant to successful trial conduct.

Finally, although this thesis successfully explored how national stakeholders can develop locally-led trial capacity, it only briefly touched upon the issues raised in the literature synthesis that question the international community's ability and willingness to invest in dedicated capacity development. Experience shows that there is inertia to considering health research capacity development to be of equal or greater value than research outputs. However, a few organisations are now flying in the face of this trend and their appears to be increasing value placed on capacity development by historically disinterested groups such as research funders, academic institutions, and healthcare journals. Like research leaders in LAMICs, current forerunners in this development field have an important role in ensuring this trend continues. If this can be achieved, the development of sustainable locally-led health research capacity in all nations could become a reality, rather than just rhetoric.

PART V: Appendices

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Case-study topic guides

Ethiopian case-study topic guides

Interview topic guide

PPT IDNO |_|_|_|_|

Gender Male/Female

Researcher Initials |_|_|_|

Date: |_|_|/|_|/|_|_| (DMY)

Recording NO ____|____

Participant Name: _____

Participant

Institution: _____

Introduction:

- ✓ Purpose of study
- ✓ Aim of interview and duration
- ✓ Who is involved and other participants
- ✓ Why participants cooperation and input is important
- ✓ What will happen with the data and how participants will benefit
- ✓ Questions?
- ✓ Receive PIS
- ✓ Consent
- ✓ Get contact details and ask for screening questionnaire to be completed
- ✓ Chance for further questions and discussion with researcher at the end
- ✓ <every time mention a problem –ask what the impact is>

Warm Up

0. Could you describe how you came to work in your current role?
 - Education, previous roles, previous institutions, interest and decision making (why choose this path)
1. Can you tell me a little bit about your current and past experiences of working in the field of clinical trials?
 - Roles/responsibilities, trial information, institution, personal experience (likes/dislikes/enjoyment)

Introduction

2. Over the years there have been more clinical trials being conducted in developing countries. Could you explain how the clinical research environment has changed in Ethiopia over the past (10)* years? *adapt for experience
 - Numbers of trials, disease areas, funders/sponsors, local/foreign
 - Why has this occurred – external (policy/capacity building/world institutional factors) or internal influencing factors (politics/war/economic growth/education)
3. Could you describe the most common clinical trials being conducted in Ethiopia?
 - Who conducts these trials - Industry / NGO / Academic / Hospital / Independent / IIT
 - Who sponsors/funds these trials - Industry / NGO / PDPs / Academic / Self/ Local / Foreign
 - Are there any clinical trials that are not common in Ethiopia? - Why is this

Core topic: IIT research

4. What is your experience with independent research and IITs? *(reiterate if previously covered – coming back to your previous experiences)
 - Have you ever led or worked on an IIT? If yes: can you tell me a bit more about that, If not: why
5. Do you think investigator initiated trials and independent research is important?
 - Can you explain why? Why is it different to other research?
 - Do you think there should be more or less?

Core topic: Operations

6. What do you enjoy most about conducting clinical trials?
 - What do clinical trials mean to you?
7. In your experience, what aspects of initiating and running a clinical trial do you find most difficult? <give participants a chance to respond>. It may be helpful if you consider the order in which you do this, starting from the earliest stages of clinical trial initiation. Let's write down the order you do your tasks on a piece of paper in the form of a flow diagram. (demonstrate a flow diagram of your daily life if participant has difficulty understanding)
<probe> Are there any situations or clinical trials that you have found particularly difficult?
 - Which – Study population / Intervention type / Study location / Urban-Rural<Probe> can you tell me more about that?

8. In your experience, is there anything different about being involved with a trial that is initiated by the local investigator?
 - How is it different
 - Are there any aspects that are particularly difficult/easier/enjoyable about this
9. What effect do you feel these problems have had on your ability to get the research done in the way you'd like to?
 - Do you think these are common problems experienced by other researchers?
10. Have you overcome any of the problems on the diagram or can you think of any solutions? Let's add these to the flow diagram.
 - Feasibility / Barriers to implementation
11. Let's think about the problems you have mentioned. Do the problems have anything in common with each other or can you suggest a source for the problem?

Core Topic: Organisational/institutional issues

12. When you need guidance on conducting clinical research or you need assistance with a problem, where do you look or where do you go to for help?
 - What type of guidance is needed
 - Source: Internet/journal/guidelines/peer or collaboration
 - How easy is it to access the information you are looking for?
 - Are there any types of information particularly hard to access? Why is this?
 - How do you think this situation could be improved?
13. What do you think are the main factors that limit independent research and the number of IITS in Ethiopia?
 - Resources (money/human/technical), trained personnel or bodies, opportunities, careers, infrastructure

<probe> can you explain that in more detail
14. Can you think of any ways to better support independent research and increase the number of IITS in Ethiopia?

Closing questions:

15. In your opinion, what are the most important areas needing clinical trial research in Ethiopia?
16. What clinical trial research would you most like to be involved in
 - Why, what role
 - Independent / IITS?
17. We are coming to the end of our discussion. It has been very helpful and has generated some great ideas.

I would like to ask for your input on the future direction of this research. What do you consider to be the priority areas that this research should address?

18. Do you have any suggestions, comments or questions that you would like to add?

Focus Group discussion topic guide

FGD IDNO |_|_|_|_|

Facilitator Initials |_|_|_|

Note-taker Initials |_|_|_|

Participant group: _____

Recording NO _____|_____

Date: |_|_|/|_|/|_|_| (DMY)

Attendees: 1. _____ 2. _____ 3. _____ 4. _____ 5. _____

6. _____ 7. _____ 8. _____ 9. _____ 10. _____

Introduction:

- ✓ Purpose of study
- ✓ Aim of FGD and duration
- ✓ Who is involved and other participants
- ✓ Why participants cooperation and input is important
- ✓ What will happen with the data and how participants will benefit
- ✓ Ground rules: -allow participants to make their own (draw on whiteboard/flipchart)
 - Only one person speak at a time – also for benefit of recording and analysis
 - Important to hear everyone's opinions. No right or wrong answers to questions – want opinions and ideas. All opinions and ideas are valuable.
 - Interested in hearing all sides of issues –positive and negative
 - Confidentiality – what is said in the room should not be shared with others
- ✓ Questions?
- ✓ Receive PIS
- ✓ Consent
- ✓ Get contact details and ask for screening questionnaire to be completed
- ✓ Chance for further questions and discussion with facilitator at the end
- ✓ **Draw seating diagram to assign notes to participants (use attendee code)**

Warm up

0. Can we go around the room and introduce ourselves, explaining where you work, your current job role and you're your experience of being involved in clinical trials.

Introductory questions

Research context:

1. Can you tell me about the most common clinical trials that are conducted in Ethiopia?
 - Disease areas / Intervention types / Classification / Phase
2. Are there any types of clinical trials that are not common in Ethiopia?
 - Why is this?
3. What institutions and organisations conduct these trials?
 - Industry / NGO / Academic / Hospital / Independent / IIT
4. Who are the most common funders and sponsor of research in Ethiopia?
 - Industry / NGO / PDPs / Academic / Self
 - Local / Foreign

Core topic: IITs

5. Can you tell me about investigator initiated trials in Ethiopia?
 - Common / Who does them / Types of studies / Research areas
6. Do you think that IITS are important?
 - Why / What advantages / Disadvantages
7. How are IITs different from industry or foreign sponsored trials?
 - Investigative areas / Purpose / Types of intervention / Study design

Core topic: Operations

8. In your experiences, what do you find are the most difficult aspects of conducting a clinical trial? We will write these down on a large sheet of paper in the form of a Mindmap.
 - Planning / Regulatory / Operational / Resources / Knowledge / Support – funding/sponsorship

<Probe> can you be specific about that? Can you give an example?
9. Can you organise or categorise these problems into groups? Let's add this to the Mindmap.

10. Are there any types of research that you feel are particularly hard to conduct? Let's add these to the Mindmap
 - Which – Study population / Intervention type / Study location / Urban-Rural
 - Why
11. Let's look at the Mindmap. Do you think that there are any problems unique to IITs or are any of the difficulties listed here that are more or less of a problem in IITs. <add this information to the Mindmap>
 - What is the effect of these difficulties?
12. Can you think of any solutions to the problems that you have identified, or have you developed solutions to problems in the past?
 - Feasibility / Barriers to implementation
13. Vignette: Suppose there is a doctor in a rural hospital in Ethiopia. He wants to conduct a simple clinical trial comparing 2 existing treatment regimens for children admitted with severe diarrhoea. How would he go about doing this?
 - Can you envisage any particular problems he may have?
 - How could he overcome these problems?
14. Now suppose he had never done a clinical trial before. How would he go about learning about how to conduct the trial?
 - Problems / Solutions
15. What do you think could be done to make his clinical trial easier to conduct?

Core topic: organisational/institutional issues

16. What do you feel are the most important research areas for Ethiopia?
 - Are these topics currently receiving attention
17. What do you think are the main factors that limit independent research and the number of IITS in Ethiopia?
 - Resources (money/human/technical), trained personnel or bodies, opportunities, careers, infrastructure

<probe> can you explain that in more detail
18. Can you tell me about how research in Ethiopia is being supported?
 - Capacity building / Training / Careers

- Do you feel that there is a difference between the quality of support for independent local research compared to commercial or foreign research?
- Can you think of any ways to better support clinical research in Ethiopia?

Closing questions

19. We are coming to the end of our discussion. It has been very helpful and has generated some great ideas.
I would like to ask for your input on the future direction of this research. What do you consider to be the priority areas that this research should address?
20. Do you have any suggestions, comments or questions that you would like to add?

Process mapping topic guide

Process Mapping Topic Guide

PM IDNO ____/____ PM ____/____ Participant sub-group: IIT / FIT

Facilitator Initials |_|_|_|_| Note-taker Initials |_|_|_|_|

Recording NO ____|____

Date: |_|_|/|_|_|/|_|_| (DMY)

Introduction:

- ✓ Purpose of study
- ✓ Aim of process mapping exercise and duration
- ✓ Who is involved and other participants
- ✓ Why participants cooperation and input is important
- ✓ What will happen with the data and how participants will benefit
- ✓ Ground rules: -allow participants to make their own (draw on whiteboard/flipchart)
 - Only one person speak at a time – also for benefit of recording and analysis
 - Important to hear everyone’s opinions. No right or wrong answers to questions – want opinions and ideas. All opinions and ideas are valuable.
 - Interested in hearing all sides of issues –positive and negative
 - Confidentiality – what is said in the room should not be shared with others
- ✓ Questions? Chance for further questions and discussion with facilitator at the end
- ✓ Receive PIS
- ✓ Consent
- ✓ Participants complete demographic information form

- ✓ Assign participants ID number
- ✓ Prepare note taking form and draw seating diagram to assign contributions to participants (use participant ID)
- ✓ Check audio device

The space provided is for brief notes to be filled in by the facilitator. For full note-taker notes,

please use the note-taking form

Before the process mapping starts:

1. Can you tell me about the clinical trial that we will be mapping?
 - Intervention/phase/sponsor/funder/design/participants?

2. Can you tell me about any previous clinical trials that this group has conducted?
 - Intervention/phase/sponsor/funder/design/participants?

Begin process mapping exercise using suitable prompts: try to include all the information on the process map rather than using additional notes.

If participants have difficulty doing the exercise, encourage them to start from the beginning and work forward towards intervention delivery.

Prompts to be used, only if the participants do not answer the questions themselves

- *Are there any other processes that you think you may have missed out? Use the Global Health Trials process map as a memory aid, but do not show it to participants because it may affect the way they draw the map.*
 - *How long did each process take?*
 - *Are there any processes that were particularly difficult? If so, why?*
 - *Are there any processes that were particularly easy, or went well, if so, why?*
 - *Are there any strategies or techniques that helped you?*
 - *Is there anything that you would have done differently with hindsight?*
 - *Is there anything you think needs adding to the process map before we finish? It may help to go through the map one last time, from start to finish.*
 - *Do you think the process map is an accurate representation of what you did to start the trial?*
-
3. How did you find this exercise? Was it easy or hard? How could it be improved? Do you think it was a useful learning exercise?

Interview topic guide

Interview Topic Guide – Sri Lanka

System based questioning

Interview IDNO: SL_____/__INT__/_

Participant specialism _____

Facilitator Initials |_|_|_| Recording NO _____|_____

Date: |_|/|_|/|_|_| (DMY)

Participant IDNO SL_____/__INT__/_ (01) (institution/method/method no. /participant no.)

Introduction:

- ✓ Purpose of study
- ✓ Aim of interview and duration
- ✓ Why participants cooperation and input is important
- ✓ What will happen with the data and how participant will benefit
- ✓ Questions? Chance for further questions and discussion with facilitator at the end
- ✓ Receive PIS
- ✓ Consent
- ✓ Participants complete demographic information form
- ✓ Assign participant ID number
- ✓ Check audio device
- ✓ <every time a participant mentions a problem –ask what the impact is

The spaces provided are for brief notes to be filled in by the facilitator when audio recording is used. When audio recording is not permitted please make extended notes on separate pieces of paper, making sure to reference the question and adding in the method IDNO and page number on each sheet of paper used.

The purpose of the interviews is to concentrate on important topics that emerged during the process mapping and focus group discussions. By interviewing participants that have an influence over these issues it may be possible to get a better understanding of the issue and explain how the present situation has formed and what keeps it in place.

Participants

The participants are likely to be leaders of research organisations or staff with a role in stakeholder institutions and research structures.

These participants may include: Leaders of research groups and academic/clinical departments, local regulators, policy makers, representatives of healthcare and research funding bodies and any other stakeholders with influence over clinical trials

Remember to ask “What effect do you feel these problems have had on your ability to get the research done in the way you’d like to?” when problems are mentioned ask “Do the problems have anything in common with each other or can you suggest a source for the problem?”

Warm Up – be brief about this. Data captured in Demographic Information Form.

0. Can you tell me about your research group/department/organisation/institution?
 - *What is its primary role or purpose?*
 - *What work is it involved in?*
1. Can you tell me about your role in this research group/department/organisation/institution?
 - *Job title and institution*
 - *Roles and responsibilities*
 - *Duties*
2. Can you describe your previous work experience and any other current positions that you hold?
 - *How did you come to work in this field?*
 - *Education*
 - *Why did you choose this field of work?*
3. **<Adapt for job role – if they have recent trials or research experience ask specifically about this. If they work in medicine or public health or politics ask more generally>**

When you think about your work experiences, what are the main challenges and opportunities that come to mind about these experiences?’

Core topic: Perceptions and values of trials – introduction of IITs

Now, I would like to hear about your opinions on clinical trials. But before we start, I want to make sure we all have a common understanding of what a clinical trial is. This is important because the use of the term “clinical trial, has recently been expanded to include behavioural and preventative care studies. The important issue is that it has an RCT design, and not the type of intervention being studied.

For the purpose of our work we use the WHO definition which is: any research study that prospectively assigns human participants or groups of humans to one or more health-related

interventions to evaluate the effects on health outcomes. Clinical trials may also be referred to as interventional trials. Interventions include but are not restricted to drugs, cells and other biological products, surgical procedures, radiologic procedures, devices, **behavioural treatments, process-of-care changes, preventive care**, etc. This definition includes **Phase I to Phase IV trials** and pharmacokinetics, even for approved standard treatment. Observational studies can be clinical trials if the participants are assigned to study arm groups by the investigator.

4. *In your opinion, what is the value of clinical trials?*

- Purpose / **What are the advantages / disadvantages** /Any trials or specific types?
Alternatives to trials?

Explain what you mean by an IIT vs FIT. Make sure everyone understands. Note that this is a LOCAL IIT.

Now I would like to hear about your opinions on IITS. But first I want to clarify what I mean by an IIT. Our definition of an investigator-initiated trial (IIT) is a clinical trial that is conceived and designed by a principal investigator or team of collaborating principal investigators in Sri Lanka and where the research is conducted in Sri Lanka. Other foreign individuals or organisations may have collaborated on or funded the project but the Sri Lankan investigator(s) remain the owners of the trial. The important thing is that the idea and plan was started by a Sri Lankan investigator. They then may have get help from other people. This is different to a foreign initiated trial where a foreign individual or organisation plans a clinical trial and then recruits Sri Lankan investigators to work on it.

5. *In your opinion, what is the value of IITs compared with other trials?*

- Advantages / Disadvantages?
 - Ownership
 - Capacity building
 - Build research culture
 - Set research agenda – locally relevant
 - Collaboration
 - Quality / status?
- Different investigative areas to other trials?
 - Purpose /Locally relevant / Types of intervention / Study design/ generation of guideline?

Research Context - make this brief or omit if short of time – important question is 10

6. *Could you tell me about the clinical trials and medical research that is conducted in Sri Lanka?*

- IITs/FITs/commercial
- Disease areas / Intervention types /Classification /Phase
- Purpose – treatment/ prevention/diagnostics etc.
- Participants and populations
- **Common/Not common – why is this, are there any types of trials or trial topics that are particularly hard to conduct?**

7. *Thinking about the research that is conducted in Sri Lanka, are there any research gaps or areas where more evidence is needed?*
 - What evidence is needed?
 - i. Novel treatment, optimisation, guideline evidence, operations, health services
 - How could these research gaps be addressed?
 - **What research would be useful for generating the required evidence?**
 - i. IITs/FITs? Other research methods?

General research structure and culture

8. **<Only ask a few senior stakeholders>** *Can you tell me about the stakeholders that have influence over clinical trials in Sri Lanka?*
 - Types
 - i. International
 - ii. Government – MOH and Educational
 - iii. Universities
 - iv. Commercial or research units
 - v. Ethics boards
 - vi. Drug and regulatory boards
 - How do these stakeholders influence clinical trial research?
 9. *A) Can you tell me about the clinical trial research culture within these stakeholder institutions?*
B) Is this the same for all stakeholder institutions or are they different? E.g. Universities, hospitals, clinics, MoH and regulatory agencies.
 - Are clinical trials important or are there other competing priorities?
 - How is research valued and what types of research are most valued?
 - Are people aware of clinical trials or exposed to them? - Are people confident to do clinical trials?
 - Is clinical trial or research training part of the curriculum? - Does training have a role in increasing value?
- C) How does this impact on the number of IITs conducted?**

General challenges and organisational/institutional solutions and support

10. *When investigators decide to undertake a clinical trial, what sort of challenges and opportunities do you think they may encounter during this process?*
 - Decisions to undertake trial? CONFIDENCE or EXPOSURE?
 - Start-up phase?
 - Conduct phase?

Core topic: Experience and institution specific questions

Why have you selected this participant? What special experience do they have that can shed light on questions and important emergent topics you have identified?
What are the emergent topics they can help with?

If you are interviewing them about their stakeholder experience think carefully about the experience specific questions and what you would like them to answer. E.g. I have noticed that ethics review is particularly problematic to investigators. Can you tell me about the ethical review process? What is your experience of it? Why would investigators have problems with it and do you think that this is justified? What causes these problems and how could the situation be improved?

If interviewing a PI about a trial experiences because they were unable to take part in a FGD

or PM exercise, use questions from the PM or FGD topic guides.

For other experiences of interest, write questions in the blank pages

Wrap up and consolidation

11. So thinking about everything we have discussed, what changes need to be made to overcome the challenges you mentioned and support and encourage more investigators to conduct IITS?

- Specific strategies
- What do you think GHT could do to try to help with this?

Close

Thank you very much for all you input. It has been very helpful and has generated some great ideas. Before we finish do you have any suggestions, comments or questions that you would like to add.

Focus Group discussion topic guide

Focus Group Discussion Topic Guide – SRI LANKA

FGD IDNO: SL____/____FGD____/____

Participant sub-group: Experienced / Inexperienced

Facilitator Initials |_|_|_|

Note-taker Initials |_|_|_|

Recording NO _____|_____

Date: |_|_|/|_|_|/|_|_| (DMY)

Introduction:

- ✓ Purpose of study
- ✓ Aim of FGD and duration
- ✓ Who is involved and other participants
- ✓ Why participants cooperation and input is important
- ✓ What will happen with the data and how participants will benefit
- ✓ Ground rules:
 - Only one person speak at a time – also for benefit of recording and analysis

- Important to hear everyone's opinions. No right or wrong answers to questions – want opinions and ideas. All opinions and ideas are valuable.
- Interested in hearing all sides of issues –positive and negative
- Confidentiality – what is said in the room should not be shared with others
- ✓ Questions? Chance for further questions and discussion with facilitator at the end
- ✓ Receive PIS
- ✓ Consent
- ✓ Participants complete demographic information form
- ✓ Assign participants ID number
- ✓ Prepare note taking form and draw seating diagram to assign contributions to participants (use participant ID)
- ✓ Check audio device

The spaces provided are for brief notes to be filled in by the facilitator. For full note-taker notes, please use the note-taking form

When taking notes, always note participant ID for each utterance.

<When listening for answers, ensure you consider whether participants are talking about IITs, FITs or general research and are they talking about an impact on start-up or just wider conduct? If in doubt...ASK!>

Remember to ask “What effect do you feel these problems have had on your ability to get the research done in the way you’d like to?” when problems are mentioned ask “Do the problems have anything in common with each other or can you suggest a source for the problem?”

Warm up

0. Can we go around the room and introduce ourselves by our first names, and let the group know about
 - a. ***For experienced participants*** - the most recent trial you have been involved in and your role on that trial
 - b. ***For inexperienced groups*** – your recent research experience and job roles
1. ***For experienced participants*** - When you think about trials that you have been involved with, or trials that you have wanted to do but not been able to, what are the main challenges and opportunities that come to mind?
For inexperienced groups – When you think about trials that you have wanted to be involved with but were unable to, what are the main challenges and opportunities that come to mind?
OR if never considered this - When you think about your previous research experiences, what are the main challenges and opportunities that come to mind about these experiences?
<Try to keep brief but use this information as examples to refer back to later>

Core topic: Perceptions and values of trials – introduction of IITs

Now, I would like to hear about your opinions on clinical trials. But before we start, I want to make sure we all have a common understanding of what a clinical trial is. This is important because the use of the term “clinical trial, has recently been expanded to include behavioural and preventative care studies. The important issue is that it has an RCT design, and not the type of intervention being studied.

For the purpose of our work we use the WHO definition which is: any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes. Clinical trials may also be referred to as interventional trials. Interventions include but are not restricted to drugs, cells and other biological products, surgical procedures, radiologic procedures, devices, **behavioural treatments, process-of-care changes, preventive care**, etc. This definition includes Phase I to Phase IV trials and pharmacokinetics, even for approved standard treatment. Observational studies can be clinical trials if the participants are assigned to study arm groups by the investigator.

2. *In your opinion, what is the value of clinical trials?*

- Purpose / **What are the advantages / disadvantages** /Any trials or specific types?
Alternatives to trials?

Explain what you mean by an IIT vs FIT. Make sure everyone understands. Note that this is a LOCAL IIT.

Now I would like to hear about your opinions on IITS. But first I want to clarify what I mean by an IIT. Our definition of an investigator-initiated trial (IIT) is a clinical trial that is conceived and designed by a principal investigator or team of collaborating principal investigators in Sri Lanka and where the research is conducted in Sri Lanka. Other foreign individuals or organisations may have collaborated on or funded the project but the Sri Lankan investigator(s) remain the owners of the trial. The important thing is that the idea and plan was started by a Sri Lankan investigator. They then may have get help from other people. This is different to a foreign initiated trial where a foreign individual or organisation plans a clinical trial and then recruits Sri Lankan investigators to work on it.

3. *In your opinion, what is the value of IITs compared with other trials?*

- Advantages / Disadvantages?
 - Ownership / Capacity building / Build research culture / Set research agenda – locally relevant
 - Collaboration / Quality / status?
- Different investigative areas to other trials?
 - Purpose /Locally relevant / Types of intervention / Study design/ generation of guideline?

Core topic: Individual motivations and enablers/barriers

4. *A) Why do people conduct IITs? What motivates them to do it?*

- a. Entrepreneurship/ innovative?
- b. Salary
- c. Time allocation for research
- d. Career recognition/status and career progression

- e. Personal development – skills and training and learning and travel/collaboration opportunities
- f. Personal interest
- g. Benefit to the organisation in terms of funding and material capacity and human capacity development
- h. Benefits to the community (refer back to what they say the benefits of trials are)

B) Can we discuss the relative importance of these factors? What are the most important incentives?

C) How do you think the motivations for working on an FIT might be different to working on an IIT?

5. *What might discourage people from conducting an IIT?*

- a. Operational difficulty – amount of work required
- b. Salary and private practice
- c. Time availability
- d. Career recognition/status and career progression
- e. Career stability and quality of life e.g. getting grants and short term work and not having tenure
- f. Personal development – skills and training and learning and travel/collaboration opportunities
- g. Personal interest
- h. Benefit to the organisation in terms of funding and material capacity and human capacity development
- i. Benefits to the community (refer back to what they say the benefits of trials are)

B) Can we discuss the relative importance of these factors? What are the biggest disincentives?

C) How do you think the disincentives for working on an FIT might be different to working on an IIT?

6. *Thinking about what we have talked about, what could be done to make conducting a clinical trial more appealing?*

- How can we maximise the incentives and reduce the disincentives so that more people will want to conduct a trial?

Core topic: practical scenario and knowledge and support

7. FOR INEXPERIENCED <or can leave this and do hypothetical start-up if not getting it>

A) Vignette: Suppose there is a doctor in a small hospital in Sri Lanka. He has never done a clinical trial before. He wants to conduct a simple clinical trial comparing 2 existing treatment regimens for children admitted with severe diarrhoea. How would he go about doing this?

- Can you envisage any particular problems he may have?
- **How would he get support and learn about how to conduct a clinical trial**

- What support is most helpful for learning the skills and knowledge required?
- **Can you explain your support** network –who helps, from where, regularity and ease – try to map it
- How could he overcome these problems?

B) What do you think could be done to make his clinical trial easier to conduct?

8. **FOR EXPERIENCED and INEXPERIENCED: Enablers and barriers to starting a trial**

In the next question I would like to talk about the start-up phase of trial conduct. This is the stage from having an idea for a trial and developing a concept to the point where the first patient receives the first intervention. Therefore it includes stages such as planning and organising the trial, securing all required resources and permissions and recruiting patients. Once the first patient receives the first intervention, we consider the next stages to be trial conduct.

A) {For experienced participants} *In your opinion, what are the most difficult aspects of starting an IIT in Sri Lanka?*

{For Inexperienced participants} *What do you expect to be the most difficult aspects of starting an IIT in Sri Lanka?*

In response to specific problems mentioned

- Is this the same for everyone or is it that you or your organisations particularly have problems with this? If so, how has this happened and what do you/they do differently?
- **What impact does this have on trial start-up?**
- **Were you able to overcome these challenges?**

B) How do these challenges, differ to the challenges that you may expect to face in the **conduct stage?**

C) How do these challenges, differ to the challenges that you may expect to face **when running an FIT?**

- Would this affect the way you have to cope with these challenges?

9. ***checklist of tasks to be done for IIT start-up***

Encourage discussion and elaboration, not just completion and filling in of exercise. Why is this the hardest, what makes it difficult or easy, is this related to that etc.

Below is a list of tasks that need to be completed when starting an investigator-initiated trial. Please look at the checklist. Can you think of anything that I have forgotten that we should add in? We can write these new tasks in the blank spaces at the bottom. Now we have a final list of tasks, I would like us to discuss the relative difficulty of these tasks. Can we place the tasks in order of difficulty please, where 1 is the most difficult.

10. *Could you tell me about the clinical trials and medical research that is conducted in Sri Lanka?*

- IITs/FITs/commercial

- Disease areas / Intervention types /Classification /Phase
- Purpose – treatment/ prevention/diagnostics etc.
- Participants and populations
- **Common/Not common – why is this, are there any types of trials or trial topics that are particularly hard to conduct?**

11. *Are there any research gaps or areas where more evidence is needed in Sri Lanka?*
- a. What evidence is needed?
 - i. Novel treatment, optimisation, guideline evidence, operations, health services
 - b. How could these research gaps be addressed?
 - c. **What research would be useful for generating the required evidence?**
12. A) *Can you tell me about the clinical trial research culture within medical institutions?*
 B) ***Is this the same for all stakeholder institutions or are they different? E.g. Universities, hospitals, clinics, MoH and regulatory agencies.***
- a. Are clinical trials important or are there other competing priorities?
 - b. How is research valued and what types of research are most valued?
 - c. Are people aware of clinical trials or exposed to them? - Are people confident to do clinical trials?
 - d. Is clinical trial or research training part of the curriculum? - Does training have a role in increasing value?
- C) How does this impact on the number of IITs conducted?**

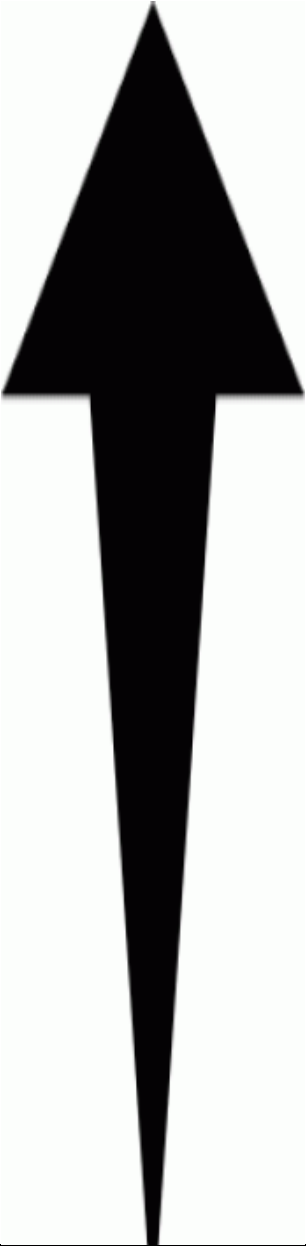
Wrap up and consolidation

13. **{For trial experienced participants}** *Many of you have successfully conducted clinical trials. What do you think helped you to do this?*
- Is this the same for everyone or is it that you or your organisation is good at doing this? If so, how has this happened and what do you do differently?
 - What do you think is important for enabling people to conduct trials?
 - What guidance could you give to others?
- {For trial inexperienced participants}** *When people successfully conduct IITs, what do you think allows them to do this?*
- a. What special situation or skills or personality do they have? VALUES AND MOTIVATIONS? Entrepreneurship/ innovative?
 - What facilitates their trials? GOOD ORGANISATIONS? OR GOOD STRATEGIES AND SUPPORT?
 - How are they different?
14. So thinking about everything we have discussed, what changes need to be made to overcome the challenges you mentioned and support and encourage more investigators to conduct IITS?
- a. Specific strategies
 - b. What do you think GHT could do to try to help with this?

Close

Thank you very much for all you input. It has been very helpful and has generated some great ideas. Before we finish do you have any suggestions, comments or questions that you would like to add?

Appendix: Tasks that impact on IIT start-up

ID No	Task checklist	ID Number in order of difficulty	
A	Thinking of research ideas		
B	Access to knowledge resources, support and guidance		
C	Writing proposals		
D	Gaining funding and sponsorship		
E	Designing the study and writing the protocol		
F	Securing ethics and administrative approvals		
G	Availability and access to suitable human resources		
H	Availability and access to suitable material resources		
I	Completing administration and logistical tasks e.g. purchasing supplies and managing budgets		
J	Setting up and running a laboratory		
K	Data management and monitoring		
L	Recruiting and managing participants		
M	Managing and training staff		
N			
O			
P			
Q			
R			
S			
T			LEAST DIFFICULT

Process Mapping Topic Guide – SRI LANKA

Before conducting this activity, get a guide to show you around the facility and orientate you first. Make note of the context.

PM IDNO :SL____/____PM____/____

Participant sub-group: IIT / FIT

Facilitator Initials |_|_|_|

Note-taker Initials |_|_|_|

Recording NO _____|_____

Date: |_|/|_|/|_| (DMY)

Introduction:

- ✓ Purpose of study
- ✓ Aim of process mapping exercise and duration
- ✓ Who is involved and other participants
- ✓ Why participants cooperation and input is important
- ✓ What will happen with the data and how participants will benefit
- ✓ Ground rules: -allow participants to make their own (draw on whiteboard/flipchart)
 - Only one person speak at a time – also for benefit of recording and analysis
 - Important to hear everyone’s opinions. No right or wrong answers to questions – want opinions and ideas. All opinions and ideas are valuable.
 - Interested in hearing all sides of issues –positive and negative
 - Confidentiality – what is said in the room should not be shared with others
- ✓ Questions? Chance for further questions and discussion with facilitator at the end
- ✓ Receive PIS
- ✓ Consent
- ✓ Participants complete demographic information form
- ✓ Assign participants ID number
- ✓ Prepare note taking form and draw seating diagram to assign contributions to participants (use participant ID)
- ✓ Check audio device

The space provided is for brief notes to be filled in by the facilitator. For full note-taker notes, please use the note-taking form

Remember to ask “What effect do you feel these problems have had on your ability to get the research done in the way you’d like to?” when problems are mentioned ask “Do the problems have anything in common with each other or can you suggest a source for the problem?”

Warm up and context

1. Can you tell me about this research institute/department/organisation?
 - *What is its primary role or purpose*
 - *What work is it involved in?*
 - i. *Any trials or research?*
 - *How is it structured?*
 - *The community it serves/patients?*
 - *Capacity, resources?*

2. Can you tell me about any previous clinical trials or research that this group has conducted?
 - *When were they?*
 - *Intervention*
 - *phase*
 - *sponsor*
 - *funder*
 - *design*
 - *participants*

3. Can you tell me about your most recent (or current) clinical trial experience?
 - *When was it?*
 - *Intervention*
 - *phase*
 - *sponsor*
 - *funder*
 - *design*
 - *participants*

4. **When you think about this trial, what are the main challenges and opportunities that come to mind?**
 - i. *Were there any particular challenges or successes?*
 - ii. *Did it go well?*
 - iii. *Did you find it enjoyable?*
 - iv. *What was your overall impression of being involved in this trial?*

In the next exercise I would like to discuss the start-up phase of your most recent (or current) clinical trial. This is the stage from having an idea for a trial and developing the concept, to the point where

the first patient receives the first intervention. Therefore it includes stages such as planning and organising the trial, securing all required resources and permissions and recruiting patients. Once the first patient receives the first intervention, we consider the next stages to be trial conduct.

5. Now we will begin the process mapping exercise. I would like you to draw a flow diagram, also known as a process map, of all the steps that you went through to start-up your most recent (or current) clinical trial. For instance, if I was drawing a process map of my day so far it might look like this (sketch a map – wake up, have a shower, eat breakfast.....). If you would like to also show the steps after the start-up phase, you are welcome to, but I would like to mostly focus on the start-up phase.

I have provided some paper and lots of pens so you can draw what you like. You can add notes with these post-it notes if you like. Do not worry if it is untidy or you forget something. We can always go back and add it later. I would like everybody to be involved as you are all experienced in at least one area of the clinical trial.

Trial conduct stage

6. Now can you tell/show me how your clinical trial went after the start-up phase?

Draw this on the process map!!

- Successes?
- Challenges?
- ***Was this stage more or less problematic than the start-up phase?***

Begin process mapping exercise using suitable prompts: try to include all the information on the process map rather than using additional notes.

If participants have difficulty doing the exercise, encourage them to start from the beginning and work forward towards intervention delivery.

Really try to drill down and get to the fine “material” detail. Who needed to sign, what stamps required, how documents were passed etc. to help understand the processes, effort required and promote discussion on the everyday menial activities required.

Prompts to be used, only if the participants do not answer the questions themselves

- ***Are there any other processes that you think you may have missed out? <Use the Global Health Trials process map as a memory aid for yourself , but do not show it to participants because it may affect the way they draw the map>***
- *How long did each process take?*
- *Are there any processes that were particularly difficult? If so, why?*
- *Are there any processes that were particularly easy, or went well, if so, why? What made this work? What circumstances led to this or facilitated this?*
- *Are there any strategies or techniques that helped you?*
- *Is there anything that you would have done differently with hindsight?*
- *Is there anything you think needs adding to the process map before we finish? It may help to go through the map one last time, from start to finish.*

- *Do you think the process map is an accurate representation of what you did to start the trial*

Enablers?

7. *Many people have trouble running clinical trials, but you have successfully ran a clinical trial. What do you think helped you to do this?*
 - *Is this the same for everyone or is it that you or your organisation is good at doing this? If so, how has this happened and what do you do differently?*
 - *What do you think is important for enabling people to conduct trials?*
 - *What guidance could you give to others?*

Lessons learnt and impact of experiences

<If short of time, only ask “What are the key lessons that you have learnt from this trial?”

8. *What are the key lessons that you have learnt from this trial?*
 - What do you know now that you wish you had known at the beginning?*
 - What advice would you give to inexperienced people who are planning to run a trial?*
9. *Do you think your experience of this trial will have an impact on your future trial work?*
 - *How?*
 - *Make changes to operations?*
 - ***Do you plan to do more trials in the future – would you like to?***
 - Why?*
 - What types of trials do you want to be involved in?*

Wrap up and consolidation

10. *So thinking about everything we have discussed, what changes need to be made to overcome the challenges you mentioned and support and encourage more investigators to conduct IITS?*
 - *Specific strategies*
 - *What do you think GHT could do to try to help with this?*

Close

Thank you very much for all you input. It has been very helpful and has generated some great ideas. Before we finish, do you have any suggestions, comments or questions that you would like to add.

BMJ Open Understanding the investigators: a qualitative study investigating the barriers and enablers to the implementation of local investigator-initiated clinical trials in Ethiopia

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To cite: Franzen SRP, Chandler C, Enquselassie F, et al. Understanding the investigators: a qualitative study investigating the barriers and enablers to the implementation of local investigator-initiated clinical trials in Ethiopia. *BMJ Open* 2013;3:e003616. doi:10.1136/bmjopen-2013-003616

► Prepublication history for this paper is available online. To view these files please visit the journal online (<http://dx.doi.org/10.1136/bmjopen-2013-003616>).

Received 18 July 2013
Accepted 24 October 2013



CrossMark

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ABSTRACT

Objectives: Clinical trials provide 'gold standard' evidence for policy, but insufficient locally relevant trials are conducted in low-income and middle-income countries. Local investigator-initiated trials could generate highly relevant data for national governments, but information is lacking on how to facilitate them. We aimed to identify barriers and enablers to investigator-initiated trials in Ethiopia to inform and direct capacity strengthening initiatives.

Design: Exploratory, qualitative study comprising of in-depth interviews (n=7) and focus group discussions (n=3).

Setting: Fieldwork took place in Ethiopia during March 2011.

Participants: Local health researchers with previous experiences of clinical trials or stakeholders with an interest in trials were recruited through snowball sampling (n=20).

Outcome measures: Detailed discussion notes were analysed using thematic coding analysis and key themes were identified.

Results: All participants perceived investigator-initiated trials as important for generating local evidence. System and organisational barriers included: limited funding allocation, weak regulatory and administrative systems, few learning opportunities, limited human and material capacity and poor incentives for conducting research. Operational hurdles were symptomatic of these barriers. Lack of awareness, confidence and motivation to undertake trials were important individual barriers. Training, knowledge sharing and experience exchange were key enablers to trial conduct and collaboration was unanimously regarded as important for improving capacity.

Conclusions: Barriers to trial conduct were found at individual, operational, organisational and system levels. These findings indicate that to increase locally led trial conduct in Ethiopia, system wide changes are needed to create a more receptive and enabling research environment. Crucially, the creation of

Strengths and limitations of this study

- To our knowledge this is the first empirical research study exploring investigator-initiated trial implementation in low-income and middle-income countries.
- Gives a compelling voice to local investigators who are often unheard in this Northern dominated discourse.
- As a formative study, the sample size was small, the sampling purposive and the findings may be context specific.

research networks between potential trial groups could provide much needed practical collaborative support through sharing of financial and project management burdens, knowledge and resources. These findings could have important implications for capacity-strengthening initiatives but further research is needed before the results can be generalised more widely.

INTRODUCTION

Many development organisations argue that clinical research in low and middle income countries (LMIC) is essential for improving public health and development.¹ In LMICs clinical research capacity remains insufficient. This perpetuates the '10/90 gap', where only 10% of global health research expenditure is allocated to diseases that primarily affect 90% of the world's population. This leads to a lack of evidence of the world's most burdensome diseases.² Evidence from Northern nations is often not relevant to LMICs,³ and its adoption into

clinical practice can be slow and treated with caution.¹⁻⁴ Increasing the number of clinical trials conducted in LMICs would help generate local evidence,⁴ which may be more likely to rapidly influence policy and practice.⁵

Most clinical trials conducted in LMICs are run by foreign research organisations with their own agendas. Recently there have been calls from within LMICs for more ownership over priority setting,⁶ greater engagement with local research communities⁷ and research conducted in line with national health strategies.⁸ Pragmatic, locally initiated disease management studies could significantly improve public health.⁹ Despite being simple and cost-effective, they are often ignored by international trial groups,⁹ and are rarely independently undertaken in LMICs. By 'pragmatic' and 'simple' we are referring to studies that are designed to test effectiveness, have few endpoints and broad eligibility criteria, thereby increasing external validity.¹⁰⁻¹¹ Meanwhile, there is increasing expectation that LMICs should take more responsibility for their research activities.¹² Increasing the number of local investigator-initiated trials (IITs) could be an answer to these issues. Several advantages of IITs over foreign-initiated trials (FITs) have been put forward (box 1).

The establishment of African-owned research centres capable of running their own clinical trials has been identified as an international priority,¹⁷ and there are ever increasing numbers of clinical trials being conducted in LMICs.⁴ However, few of these trials are locally initiated,¹⁸ and globally, trials are becoming harder to implement.⁴ Many research bodies have increased efforts to support IITs in Europe,¹⁸⁻¹⁹ but within LMICs capacity building mostly focuses on developing sites to run international trials. Capacity building to support independent locally led trials is likely to require a different approach. However, little is known about the best way to develop capacity and facilitate their conduct. This formative study investigates the issues facing local trial investigators in Ethiopia, and was designed to begin addressing this knowledge gap by determining the barriers and enablers to trial conduct.

Box 1 Advantages of investigator-initiated trials over foreign-initiated trials

- ▶ More applicable to local populations due to building on local healthcare knowledge¹³
- ▶ More demand-led and responsive to a country's needs because they are driven by a national agenda⁹
- ▶ More likely to influence policy¹³ and sustainably link research to action¹⁴
- ▶ Often simple studies that address important topics such as disease management⁴⁻⁹
- ▶ Involve local staff at all levels and stages of trial conduct,¹⁵ so there is more opportunity for 'learning by doing' and skill development¹⁶

METHODS

We conducted a qualitative study using in-depth interviews (IDIs) and focus group discussions (FGDs). Research exercises took place in Addis Ababa and Gondar, Ethiopia, in March and April 2011. Ethiopia was selected to represent a country in Sub-Saharan Africa that conducts a modest number of clinical trials while having sufficient trial experience to contribute to this study. Ethiopia had 39 trials registered at the time of fieldwork; a breakdown of these by intervention and sponsor is shown in figure 1. The majority of drug trials investigated the use of approved drugs to optimise treatment.

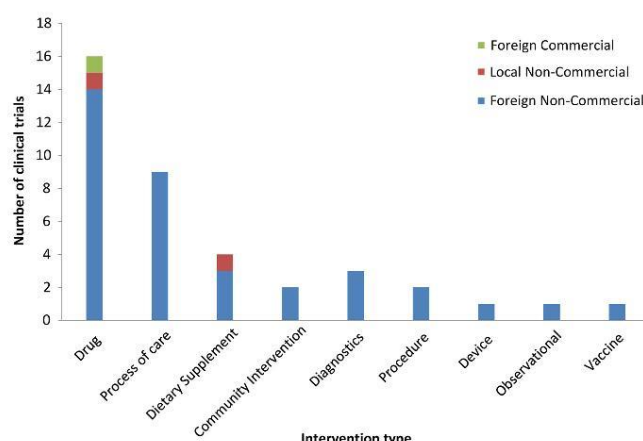
This study seeks to understand the perspectives and experiences of current and potential trial investigators and staff. Owing to the paucity of previous work on this topic, we did not prospectively adopt a specific theoretical framework. However, research questions were influenced by the fields of organisational change and development. FGDs and IDIs were semistructured and explored the following themes: the clinical research environment in Ethiopia, barriers and enablers to trial conduct, access to appropriate skills and knowledge, current support for clinical trials and recommendations for change. Questions were tailored to participant experience and emerging themes.

Participants were identified first through trial registration searches and subsequently by snowball sampling from these individuals. Health researchers with previous experiences of clinical trials or stakeholders with an interest in trials were selected. Of all the participants approached, none refused to take part. Interviews and discussions were conducted in English, and explored key points until no new information emerged. In preliminary meetings, participants said they would speak more openly if discussions were not audio recorded. This was because they would be uncomfortable criticising partners or regulatory bodies while being recorded. One participant explained that this worry was a result of the legacy left by previous authoritarian regimes. Detailed notes were taken with quotes noted as near verbatim as possible, detailing identification numbers.

This study was approved by the University of Oxford Tropical Research Ethics Committee. Verbal informed consent was obtained from all participants and review of discussion contributions and written confirmatory permission was obtained for all participants who could be contacted (15/20). No quotes are included from those who could not be contacted.

Notes were analysed by thematic coding analysis using Nvivo qualitative data analysis package (QSR International Pty Ltd. V.9, 2011) to help organise the data. Data were coded inductively according to its semantic content.²⁰ Using relationship and modelling functions, a mechanistic model of factors influential to clinical trial conduct was developed through the piecing together of complementary segments of data contributed from different participants. Coding was completed

Figure 1 Number of clinical trials in Ethiopia by intervention type and sponsor, as registered on the WHO International Clinical Trials Registry Platform in the same period as data collection (30 April 2011). The observational study was registered as a clinical trial but was a cohort study with a nested cross-sectional design.



by SF with consultation and agreement from other authors (TL, CC and BA). Findings were reviewed and commented on by all authors.

RESULTS

Study population

We conducted two FGDs and six interviews in Addis Ababa and one FGD and one interview in Gondar. A total of 20 researchers participated; seven were based at a research centre, one at an NGO, eight at a hospital and four at a university. Participants had varied job roles. Those currently working on a clinical trial included: senior investigators (n=2), trial managers and coordinators (n=5), laboratory personnel (n=5) and research nurses (n=2). We also recruited six medical

researchers not currently working on a clinical trial, three of whom had previous trial experience and three that did not. The participants had experience in a diverse range of medical professional experience domains (figure 2).

A role for investigator-initiated trials

All participants reported that too few clinical trials are conducted in Ethiopia, and felt this limited the ability for guidelines to be based on local evidence. Most treatment strategies were based on international guidelines, which many participants thought could be inappropriate. Participants proposed that locally-led trials would be useful for filling this evidence gap and that the conduct of simple design studies was independently achievable. Many researchers would like to lead their own studies and had important questions, but were often unsure of how to go about doing this, as described by this senior clinician:

We don't have the evidence to change local practices but we definitely know some written guidelines don't work. There are a number of unanswered questions for trials but we don't know how to do them. We need clinical research [in disease areas] that has a different effect in Ethiopia, for example HIV and TB. These diseases are similar as to other places but we have had little success [controlling them] here. So why? Where are the mistakes? These sorts of investigations are easy, they would support awareness and fill gaps. FGD—3 PPT—1

Compared to foreign-led studies, local trials were perceived to be more likely to address evidence gaps, be more useful for developing treatment guidelines and more sensitive to community issues. One junior clinician described this through his experiences:

Investigator-initiated trials increase evidence, particularly locally relevant evidence. For instance the Leishmania

Medical professional experience domains	Number of participants with experience (one participant may have multiple experience domains)
Clinical trial experiences	
No clinical trial experience	3
Foreign initiated trials	15
Local investigator initiated trials	3
Other experiences	
Academia	8
Clinical Practitioner	9
Public health practitioner	3
University research leadership	5
Ethics board member	3
Government worker	1

Figure 2 Participant experience of different medical professional experience domains. Experience domains are not mutually exclusive and one participant can have multiple experience domains.

strain in Gondar seems to be a bit different to the other strains because the drug treatment is working better in the other areas. This will prevent mistakes in clinical care. INT—6 PPT—1

Human and material capacity

While a general lack of materials, infrastructure and laboratory facilities were thought to reduce the number and scope of trials, most participants felt that human resources were the critical factor. Respondents stated that there were too few investigators with the technical expertise to initiate a trial. There was also a shortage of skilled research staff, with one investigator stating that if one or two staff left, their trial could not continue (FGD—3 PPT—1 senior clinician and trial investigator). This lack of expertise and research skills was blamed on minimal research focus in clinical education, few opportunities to gain experience and few local experts who could share their knowledge.

From my undergraduate experience, I was trained to be a clinician and not a researcher; this is from a curriculum point of view. Few clinicians use clinical trials as they are involved in primary care and not research. They have no spare time to think about research... We need the opportunity to have a simple role and experience to get more people to do more trials. As more people get involved in simple research and trials, more research will be done. INT—6 PPT—1, trial clinician

Individuals skilled in trials were often too busy with regular duties to be able to conduct research. Most senior trial staff were clinicians and while release from routine duties could be negotiated, they complained that healthcare tasks still had to be prioritised. Academics had allocated time for research but this was regularly cited as insufficient. The limited manpower allocation to research and few opportunities to gain experience resulted in a negative feedback loop, as explained by this trial clinician:

The scope of activities is narrowed by the time and economic constraints and the fact few individuals can be involved. Because the scope is narrowed this results in a cycle of fewer people being involved, which in turn results in less motivation, fewer trials and less exposure and realising the way of thinking and less achievement. Then less people are involved and there are fewer trials. INT—6 PPT—1

Regulatory and other administrative bottlenecks

Respondents reported that complex and strict government regulations made it very difficult to investigate novel interventions and recruit vulnerable populations. Regulatory and ethical review times also introduced delays and it was not uncommon for grants to expire before all approvals were in place. A trial principal investigator (PI) explains this further:

Regulatory authorities have no clear guidelines so it is problematic getting approvals. They are also not experienced enough and so are overcautious and they cannot decide on interpretations. FGD-1 PPT-1, Trial PI

Ethics committee members admitted that limited resources, knowledge gaps and membership shortages slowed review times, but also pointed out that poor quality applications meant resubmission was regularly required. They emphasised that clarification of regulations and developing review capacity were essential to facilitate trial implementation and that more training in research ethics was needed. One participant explained that The Ethiopian Bioethics Initiative is already working towards this. Funded by the European and Developing Countries Clinical Trial Partnership, The Ethiopian Bioethics Initiative helps research sites to form Institutional Review Boards (IRBs) and train the committee members on basic principles of ethical clearance. Under this grant they have established and trained 11 IRBs.

University and government administration systems were unanimously regarded as overly complicated and blamed for many operational delays. To cope with this, many investigators said they required an administrative assistant but could not afford one.

The university finance department is a bottleneck. You really need an admin assistant to help with this. Most doctors do not want to go through the pain of organising and administering all this. Also if you do not report your annual budget on time you may be penalised and have your salary suspended. The clinical trial financing really increases the amount of work you must do for your budget reporting. If I got a good grant I would hire an admin or research student to manage these issues. INT—3 PPT-1, clinician

Operational hurdles

During one in-depth interview, a process mapping exercise was used as a template for discussion; the participant draws a detailed flow diagram of the steps and tasks involved in conducting their clinical trial, noting problems, successes and changes to be made in hindsight. Box 2 describes the experience of one PI, providing an example case of operational hurdles and the importance of advanced planning.

The majority of serious operational difficulties occurred during the start-up stage of trial conduct. Once intervention delivery began, there were few major challenges. Participants attributed most operational hurdles to wider issues. The main operational hurdles and their causes are summarised in table 1. Operational enablers included: keeping trial designs simple, only investigating approved interventions and non-vulnerable populations to prevent regulatory delays, and rapid recruitment of participants due to large patient pools that were usually prepared to give consent.

Box 2 Experience of a local principal investigator (PI) on a foreign non-government organisation-led non-commercial study

Registering the clinical trial caused considerable delays because task allocation was overlooked. Ethical approval for this relatively complex study took 12 months due to a cycle of resubmission. Ordering to delivery of supplies routinely took 3–6 months. Data entry and analysis were delayed because the data management system had not been considered early enough and training could only be obtained in Europe. Some laboratory tests were outsourced to a local private laboratory because staff lacked the training and equipment, while other assays were complicated by lack of normal ranges for local populations. In hindsight the PI would have taken more care with planning and preparation and made roles and responsibilities clear from the outset.

Initiating an idea: awareness, confidence and motivation

Participants reported that limited awareness of trial research among their colleagues was a common reason for trials not being attempted. This was because potential

investigators were not exposed to the methodology or had not considered doing them, as explained by this PI:

People do not have the vision that clinical trials will improve patient care because they do not see it in their daily lives. Clinical trials are important but essentially people do not see them enough to think of them.
INT—4 PPT-1, senior clinician

This was attributed to omissions in medical student curricula, limited access to literature, little trial research training and few trial opportunities. If individuals had considered conducting a trial, many participants said that most researchers were not confident to initiate one themselves because they lacked the knowledge and skills. Even investigators who had considerable experience on foreign-led studies said they did not feel ready to lead their own. The expectation of operational difficulties and few examples of role models successfully conducting trials created a 'phobia' of trial research, with people believing them to be almost impossible. This 'phobia' and lack of awareness was seen as a key barrier to trial conduct, as explained by this junior trial investigator:

We need to develop and support a research culture by capacity building to develop skills and resources, not big capacity building like an operating room, but small scale like small grants for beginner researchers to do research and get practice—this would take away the phobia of writing proposals and publications. When the phobia has gone there will be floods of research. We need to open our eyes and see what can be done. For instance people don't know how to write a proposal. In people's academic studies this sort of stuff is not given priority. Even small research will be an eye opener and the phobia will be gone. FGD—3 PPT—2, clinician and junior investigator

Even when potential investigators felt ready to conduct a trial, many participants said that the motivation for undertaking them was insufficient and this discouraged their colleagues from attempting them. Participants were encouraged by altruistic incentives such as community health improvement and organisational development but personal career incentives were weak. A lack of research career options discouraged students from entering into research after studies or caused them to migrate for work, as this junior academic explained:

We need to make sure people get jobs and an established career in research to get them to stay in their home country or to come back to their home country after training or education abroad. INT—2 PPT-1

Researchers also reported little recognition for research and that promotion could be achieved without doing research. Additionally, strong salary and workload disincentives were cited, as summarised by this IDI participant:

Table 1 Participant reported operational hurdles and their causes

Operational hurdles	Reported causes
1. Difficulty writing proposals and gaining funding	▶ Little local funding, competitive international funding ▶ Technical ability and confidence lacking ▶ Unsure of funding process; investigators do not complete application ▶ Lack of training
2. Slow regulatory and ethical approvals	▶ Complex and unclear guidelines ▶ Limited ethical review capacity ▶ Poor-quality submissions
3. Problems with trial management	▶ Lack of experience and poor planning
4. Burdensome administration and difficulty purchasing supplies	▶ Complex and slow systems ▶ No administrative support
5. Problems with setting up and running laboratory tests	▶ Limited funds and facilities ▶ Difficulty purchasing supplies ▶ Lack knowledge in technologically advanced procedures

The problem is that this [clinical trial research] will take lots of your time and while it is possible to reduce your clinic hours, this means you would lose money. The country does not pay you even though it is for public benefit. There is no incentive, in short". INT—4 PPT -1, senior clinician

The key enablers: training, knowledge sharing and experience exchange

Equal to their value for building technical competence, many participants saw trial training, knowledge sharing and experience exchange as 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 boosted a researcher's confidence that trials were achievable and experience exchange was important for raising professional standards and dispelling what one respondent termed 'pseudo-confidence' (INT—4 PPT-1—Clinician and trial PI); meaning to continue working in a suboptimum way because knowledge of more rigorous methods was lacking. Many participants emphasised that all these enablers would be more effective if grounded in local examples and context, such as knowledge sharing with individuals whose settings were similar to the researcher's own. Learning activities were also highly motivational because they were prized for both personal and professional development. Given the scarcity of trial opportunities in Ethiopia, some participants suggested that national or international experience exchange programmes would be useful. One FGD participant explained her trial team's experiences:

What we really want is for a south-south collaboration like Kenya or Uganda to do exchange placements for our junior staff. This would show people in resource-limited settings it is possible to do trials and would motivate people much more than website or e-learning...She [referring to research nurse] has been to Kenya and Switzerland and this has helped her to see how clinical trials are done and what is good and bad and see the possibilities. FGD—3 PPT-1, senior clinician and trial investigator

The importance of collaboration

While some respondents had negative experiences with foreign led-studies or said they would prefer to be less dependent on foreign groups, most participants were very positive about international collaborations, assuming intellectual independence could be protected. Technical expertise and infrastructure strengthening provided through collaborations were consistently proposed as a solution to the limited human and material resources. Particularly, collaborative grant applications had been very helpful for securing funding by increasing the quality and credibility of applications. Local and international collaboration was also seen as a key way to access and promote training, knowledge sharing and

experience exchange. This senior academic summarises the general opinion:

The priority is addressing local concerns like field-based optimisation. Weight should be given to locally initiated ideas. However, you should then ask for international assistance and collaboration. The investigator-initiated trial is all about the idea and not about the operation. You do not have to re-invent the wheel; you should make the most of global knowledge and skills. Everyone should chip in with their appropriate competence and expertise. This way the work will be faster and more efficient and local researchers will have access to technologies. INT—1 PPT-1

However, junior participants said they lacked the contacts and knowledge to develop partnerships and even established researchers often felt intellectually isolated from the East African and wider research community. This was believed to hamper innovation and cause repetition of ideas.

DISCUSSION

This study highlights that Ethiopian investigators think that investigator-initiated trials would generate highly useful and applicable data, supporting the call for more local evidence generation in LMICs. The challenge is implementing and successfully conducting a locally led study. We have identified barriers to the implementation of investigator-initiated trials in Ethiopia at all levels of the research system. Exploring through the perspective of local investigators has given a critical understanding of how these issues influence their ability to initiate trials. We have demonstrated the importance of training, knowledge sharing, experience exchange and collaboration, for breaking down barriers in somewhat unexpected ways and now consider, in light of this, how locally-led trials can be better supported.

The research system

Health research systems represent the coordinated activities of all stakeholders to produce health research and may operate at local, national, regional or global levels. The four main functions of health research systems are: stewardship, financing, resources and producing and using research.²¹ In Ethiopia, barriers and enablers to trial conduct have been identified at all levels of the national research system; system, organisational and individual. The main influential factors identified in this study have been summarised into a mechanistic model (figure 3). The following description is intended to illustrate the interconnected nature of the barriers to trial research and how deficiencies at one level can have cascading negative effects. System level barriers impact on all levels through often dysfunctional regulatory and administrative systems, insufficient funding allocation and limited ethical review capacity. Suffering from limited resources, the organisational level provides

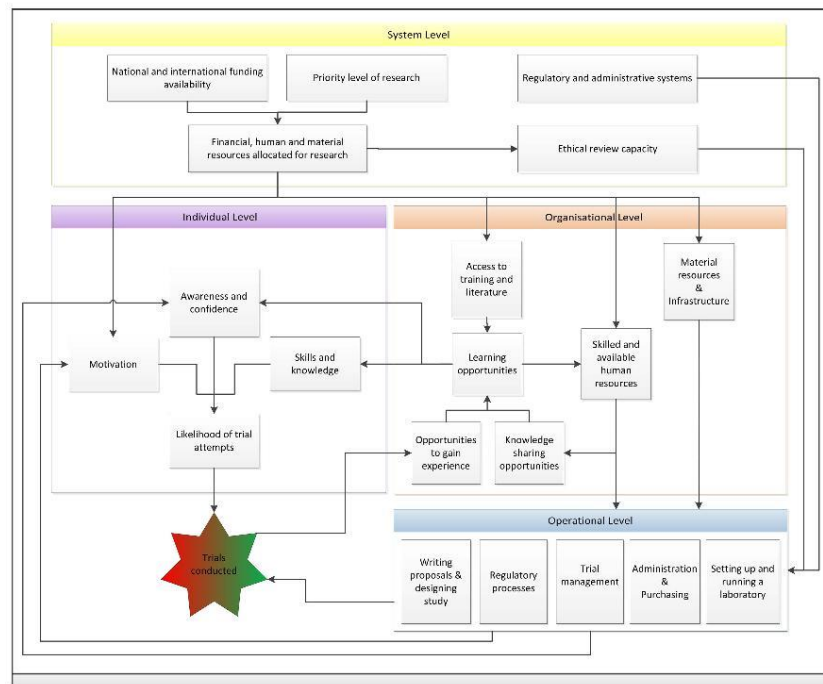


Figure 3 Mechanistic model of the factors influencing clinical trial conduct in Ethiopia.

limited learning opportunities, which negatively impacts on human resources. These deficiencies, combined with adverse regulatory and administrative systems, make operating clinical trials difficult. The combined effects of insufficient resources, limited learning opportunities and difficult operations result in a disabling research environment at an individual level. This reduces awareness of trials, limits competence and confidence and reduces motivation to undertake them. Few trials are attempted and this forms a negative feedback loop by reducing opportunities for experience.

A detailed review of the Ethiopian Health Research System also cites slow regulatory and ethical review, difficult administration systems, limited human resource allocation and few incentives as major impediments.²² However, it is important to emphasise that our description is not universal and individual examples of enabling practices and trial capacity exist. Furthermore, no information was available to us on the number of trial applications, rejections and turnaround times and although little local evidence-based practice was reported, this was not confirmed by the authorities and examples of local trials influencing policy are found in the literature.²³ Nevertheless these results demonstrate the importance of taking a system-wide view to research development.

Operational problems are embedded in wider issues, and while certain strategies may help investigators cope with problems, their resolution is dependent on strengthening the capacity at all levels of the system. Fortunately in-country expertise exists in almost all major aspects of the health research system, which should greatly facilitate strengthening efforts.²²

Building a receptive research environment

Although the capacity to conduct trials was limited, most researchers agreed that simple design studies could be carried out. However, local investigators have attempted few trials. A key problem was the disabling research environment at the individual level. Clinical trials are a relatively new phenomenon and are not yet embedded in the Ethiopian research culture. Therefore, their implementation can be viewed as a change within this culture. The Awareness, Desire, Knowledge, Ability and Reinforcement (ADKAR) model for organisational change management, suggests that for a change to happen at an individual level, ADKAR must be present.²⁴ Trial awareness was limited and investigators did not have the vision that trials would improve patient care. Although most participants had the desire to lead a trial, they reported a general lack of knowledge and

competence. For those that had the knowledge, many still felt unable to lead a trial, or were unwilling because of minimal motivational reinforcement.

This study, and others,^{25–26} suggests that increased learning opportunities and rewarding career paths are required to increase human resource capacity and retain skilled personnel. Increasing research components in taught courses, and providing training and small research grants for young researchers would increase awareness, desire and knowledge to conduct research. In Ethiopia, clinical academic staff have low salaries and are paid less than public sector physicians.²⁷ This, combined with limited funding, high-teaching burdens, low-quality facilities and frustrations with bureaucratic and operational hurdles found in this and another study,²⁷ all serve as strong disincentives to research. Providing protected time for research and recognising research within careers would help motivate investigators to undertake trials through positive reinforcement, but this alone may not be sufficient without adequate salaries to offset lost revenue from private practice and consultancy work.

Several participants expressed their inability to lead their own trial as a lack of confidence, or phobia and investigators who had worked on foreign-led studies still did not feel ready to lead their own trial. Local funding and material capacity constraints were often cited as the cause, but many researchers had not applied for international funding. Expectation of insurmountable barriers and lack of successful role models certainly reduce confidence. However, it is possible that the intellectual isolation identified in this and another study,²⁷ and lack of a supportive research environment, could reduce initiative. We also propose that previous regimes that actively discouraged autonomy, could have left a legacy that reduced the ability of individuals to act as agents in change.

Networking

Collaboration was key to the provision of training, knowledge sharing and experience exchange and accessing technical expertise and infrastructure strengthening. Better networking within and between local and international research organisations could facilitate the provision of these enablers, decrease intellectual isolation and help develop a National Health Research System.²²

Successful local sites are often busy, so exchange placements could be organised to allow more individuals to get involved. This could potentially increase trial staff numbers and reduce the impact of task shifting on clinic work. This may then reverse the negative feedback loop between insufficient human resources and few trials. Local research networks could support sustainable training models if a few experts become trainers of trainers and mentorship programmes linking experts to junior staff could provide inspirational support and guidance for isolated individuals. The need for administrative support in LMICs is common as many universities

lack established research services.^{26–28} Cooperation between departments to form research clusters would make hiring an administrative assistant affordable and could help share the cost and burden of purchasing supplies.

The creation of communities of practice could help to develop these relationships but proven strategies that foster their development are not clearly established.²⁹ Networking opportunities such as workshops would be useful, but first, all stakeholders need to be identified, and travel, time and cost can be barriers. Also, the informal nature of partnership formation in this study meant that less established researchers did not have the contacts or knowledge to find partners. One solution could be to develop a local and international online networking facility, detailing research interests, expertise, resources and current projects.

Prioritising research systems

Capacity building attached to foreign-led studies typically focuses on training individuals in specific skills or providing one specific service or resource. While this may get a particular study completed, in Ethiopia, it does not appear to provide the package necessary to allow local investigators to conduct their own trials. This study demonstrates the diversity of factors influencing IIT implementation and shows that focusing on system wide improvements must be integral to any long-term research development plan for Ethiopia. For this to happen, we suggest that research must be prioritised, not just in terms of resource allocation but also the value placed on research. However, in a country with insufficient health workers to provide routine health-care²⁷ and many other competing priorities, this may be difficult.

Despite this, such a value change could already be underway. The Ethiopian Science and Technology Agency devised strong implementation strategies to support research in 2006³⁰ and built on them in 2012.³¹ The importance of research and developing research capacities is now central to the Ministry of Health strategy, and local trial data³² has influenced policy.³³ Recommendations for fostering a research culture in the New Public Universities have been developed³⁴ and the Jimma University in South West Ethiopia has been applauded for pioneering new innovative teaching methods, valuing research within institutional culture and integrating it in career progress.^{27–35} Meanwhile, The Ethiopian Bioethics Initiative is working hard to strengthen regulatory procedures and provides a successful example of developing ethical review capacity.

Strengths and limitations

As a formative study, the sample size and range of stakeholder roles was small, and the findings may be specific to the locations or dependent on contextual factors such as governance style. Although this limits the breadth of perspectives and generalisability of findings, the study sample

accessed diverse experiences and used in-depth qualitative methods to uncover issues in a largely unexplored area, while giving a compelling voice to local investigators who are often unheard in this Northern dominated discourse. The inability to audio record the discussions may have had some impact on the accuracy of the notes taken. However, we felt it was more important to ensure open and frank dialogue, and the detailed notes were subsequently reviewed by participants to ensure accurate representation. The recommendations in this study are congruent with those proposed by The Ethiopian Ministry of Science and Technology,^{30 31} and also agree with much of the current international literature. This includes the key factors for enabling a research environment as identified by The Health Research System Analysis Initiative of WHO/RPC,²¹ and recommendations for increasing investigator-initiated trial conduct by The European Science Foundation.³⁶ Nevertheless it was important to confirm that local investigators in LMICs held similar views as espoused by the above reports. Our subsequent research on this topic has been conducted in other settings, including a wider range of stakeholders in order to overcome these limitations.

CONCLUSION

Developing research capacity to conduct investigator-initiated trials is multifaceted and likely to require a different strategy to traditional approaches that focus on individuals or capacity building for specific studies. An appreciation of the barriers and enablers at all levels must be central to development drives. While this study provides a preliminary step forward in this area, further work is needed to test these findings in other settings and to develop the thorough understanding required to successfully support these critical studies.

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Acknowledgements The authors would like to thank all the faculty, researchers and students who participated in the study in Ethiopia.

Contributors SF conceived, designed and implemented the study, analysed the data and drafted the manuscript with input and assistance from CC, BA and TL. FE, SS and JA collaborated on the interpretation of data and critically revised and reviewed the manuscript. All authors approved the final version of the manuscript.

Funding This work was supported by The Global Health Network, a Bill and Melinda Gates Foundation funded project (grant reference: OPP1053843), and in part by a Nuffield Department of Medicine Doctoral Prize Studentship. The funders had no role in study sponsorship.

Competing interests None.

Ethics approval This study was approved by the University of Oxford Tropical Research Ethics Committee (OXTREC Reference 70-11).

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement No additional data are available.

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25/10/2013

Barriers and enablers of locally led clinical trials in Ethiopia and Cameroon: a prospective, qualitative study: The Lancet



THE LANCET

The Lancet, [Volume 382, Issue](#), Page 14, 20 October 2013
doi:10.1016/S0140-6736(13)62175-3

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Barriers and enablers of locally led clinical trials in Ethiopia and Cameroon: a prospective, qualitative study

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Abstract

Background

Clinical trials provide gold standard evidence for policy. Local investigator-initiated trials could generate highly relevant data for national governments of low-income and middle-income countries, but too few are done and information about how to facilitate them is scarce. We identified barriers and enablers to such trials in Ethiopia and Cameroon.

Methods

Our multisite, prospective qualitative study—done in Ethiopia and Cameroon—consisted of in-depth interviews (n=22), focus group discussions (n=9), and process mapping exercises (n=7). Local health-researchers with varying trial experience, senior stakeholders, and regulators were recruited through snowball sampling (n=72). Approval was obtained from home, local, and national review boards and verbal or written consent was obtained from participants. We assessed data by thematic analysis.

Findings

System and organisational barriers to trial conduct were similar between Ethiopia and Cameroon: low resources, weak regulatory and administrative systems, few learning opportunities, little human and material capacity, and few incentives for doing research. In Ethiopia, lack of awareness, confidence, and motivation to undertake trials were key individual barriers, but in Cameroon, environments that discourage personal initiative were more problematic. Learning opportunities and international collaboration were important enablers in both countries, but encouraging more active involvement of researchers at all stages of the trial process facilitated trial undertaking in Cameroon especially.

Interpretation

In addition to context-specific issues, we have shown the existence of perennial organisational and system barriers in Africa. These findings indicate a common need to make system-wide changes and build receptive research environments for researchers in low-income and low-to-middle-income countries.

Funding

The Global Health Network (Bill & Melinda Gates Foundation), Nuffield Department of Medicine Doctoral Prize Studentship.

Contributors

SRPF designed the study with input from TL, CC, BA, and JA. SRPF collected the data with assistance from JA. SRPF analysed the data and wrote the abstract with input from TL and CC. All authors have seen and approved the final version of the abstract.

Viewpoints



Strengthening Neglected Tropical Disease Research through Enhancing Research-Site Capacity: An Evaluation of a Novel Web Application to Facilitate Research Collaborations

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Background

The increasing number of clinical trials in developing countries brings unique challenges, including highly customised research infrastructure and narrow research focus. Many research sites have been equipped for one specific trial or disease area, often for a particular sponsor, with little consideration to subsequent diversification or sustainability [1–4]. Furthermore, the diseases studied in developing countries are seven to eight times more likely to be of relevance to developed countries than to developing countries [5,6]. Accordingly, research sites are often only equipped to carry out research on diseases that are most relevant to developed nations—for example, noncommunicable diseases—rather than addressing local priority issues [7,8].

There is further discrepancy between the amount of research conducted on neglected tropical diseases (NTDs) when compared with “the big three”: human immunodeficiency virus (HIV), malaria, and tuberculosis (TB) [2]. One 2013 report estimates that only 1% of global spending in research and development is related to NTDs [5].

To foster research in NTDs and local disease priorities, it is important that research sites equip themselves with the skills, confidence, and knowledge to lead locally relevant research, not just in the conduct of clinical trials for the registration of new drugs and vaccines, but also in diagnostics, surveillance, disease management, and implementation science. Increasing the scope and diversity of investigations undertaken by research sites would contribute substantially to increasing the evidence base for diseases most

relevant to developing countries, particularly NTDs [9].

Many partnerships aim to pool resources and support researchers by equipping them with the skills and knowledge to initiate their own research, including the World Health Organization's Tropical Disease Research Fellowship Scheme (WHO-TDR), European and Developing Countries Clinical Trials Partnership's (EDCTP's) Networks of Excellence, and free online resources such as the Global Health Network (www.theglobalhealthnetwork.org) [10,11].

However, as reported by one eminent Central African researcher, there is still a gap in terms of enabling local researchers to make themselves known to other researchers: “There is no system or database where you can actually go and say, ‘In [my country], we can get this number of toxicologists and they are in these institutions or in this establishment.’...In Africa, people don't know each other exist and so cannot maximise resources and cannot work together.”

When asked about how such problems could be overcome, numerous sites reported the need for an online tool that would allow them to highlight their experience for potential collaborators. For example, one responder stated that they thought “having an online database would be a great way of finding collaborators,” and another response indicated a need for “a platform to collaborate with stakeholders; [and] wider dissemination of opportunities.” No such tool or platform has previously existed, meaning that the skills and knowledge of research sites are effectively isolated.

A related frustration reported by research sites after a project concludes is the inability to find new studies to work on, meaning that sites often lose their trained staff as soon as their study-specific funding ends. This lack of access to new research collaborations is a major obstacle for those aiming to follow a career in research, as well as for sites, which frequently lose the capacity they have built up. Increasing the visibility of these sites will promote greater

Citation: Furtado T, Franzen S, van Loggerenberg F, Carn G, Grahek S, et al. (2014) Strengthening Neglected Tropical Disease Research through Enhancing Research-Site Capacity: An Evaluation of a Novel Web Application to Facilitate Research Collaborations. *PLoS Negl Trop Dis* 8(11): e3225. doi:10.1371/journal.pntd.0003225

Editor: Alejandro Javier Krolewicz, Instituto de Investigaciones en Enfermedades Tropicales Universidad Nacional de Salta, Argentina

Published: November 13, 2014

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Funding: This report is based on research funded in part by the Bill & Melinda Gates Foundation. The findings and conclusions contained within are those of the authors and do not necessarily reflect positions or policies of the Bill & Melinda Gates Foundation. The funders had no role in study design, data collection and analysis, or decision to publish. The funder had the opportunity to review the manuscript during publication.

Competing Interests: The authors have declared that no competing interests exist.

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site sustainability and long-term support for research staff through improving access to diverse research experiences. The stability and accumulated knowledge, confidence, and training will ultimately help researchers improve site infrastructure and skill bases, thus enabling them to initiate their own research into local health issues [4,5,10,12]. For example, strengthening the capacity of Africa-owned clinical trials to allow countries to pursue their own research and development (R&D) agendas has been identified as an international priority by WHO [4,12–14].

Interestingly, sponsors and funders also experience difficulties in locating research sites with which to work. There is no publicly available global directory of sites or easy means of locating new partners. As a result, they often collaborate with the same research sites for each disease area, furthering this lack of diversification at research sites [14].

Against this background, a clear need emerged for a formal mechanism allowing established research sites and interested new researchers to promote their skills, facilities, staff, and experience to those planning studies. In response to this need, the Global Health Network has provided a resource called Site-Finder, a free and open-access online application. Adapting technology from dating websites, the application allows research sites to have an online presence and automatically suggests research collaborations between research sites and new research studies that have been posted on the site. The application has now been built, pilot-tested, and launched, and it is running successfully.

Methods

Site-Finder was developed in 2012 by the Global Health Network, in collaboration with a working group comprising 13 members from the Bill and Melinda Gates Global Health Clinical Consortium, a collaboration of product development partnerships (PDPs) working in various areas of neglected tropical diseases and diseases of poverty research. The application was built and prepiloted on a staging site with the PDPs and eight research sites. Following revisions, a second iteration was released online in pilot format in November 2012, and research sites and groups planning studies were invited to sign up. Monitoring through constant online technical support was performed to identify and rectify any issues, and the final version was launched in June 2013.

After three months of online usage, an interim evaluation was performed in which registered research sites were sent a nine-item questionnaire via email. The questionnaire used a mixture of open-ended questions and rating scales to assess the ease of use, concept, need, and technical support of the Site-Finder application. Site-Finder was released formally in July 2013 and has been functioning successfully since then.

Results

Feedback from sites responding to the interim evaluation ($n = 16/50$ or 32% of sites) was positive: 100% of users marked the concept of Site-Finder as “very good” or “good,” 81.3% of users rated Site-Finder “easy” or “very easy” to use, and 90% marked that they felt Site-Finder provided adequate support to those entering information about their sites.

In terms of motivation, all sites that responded to the questionnaire mentioned wanting to find additional research collaborations for their sites, with one also wanting to share its own experiences with other sites.

During the six-month pilot phase, 52 research sites across 19 developing countries registered with Site-Finder, along with ten research projects seeking sites. The research sites represented great diversity in size and type, including large-scale national research institutes as well as small investigator-led sites at hospitals. Similarly, good diversity was shown in the research studies added: a mix of noncommercial organisations or universities and a range of disease areas and study types. Site-Finder continues to grow post-pilot phase, having received over 6,300 visits from over 3,000 users, across 142 countries (3 June 2014). Twenty studies and 110 research sites have registered (see Figure 1), and user reports of sites contacting one another and of studies making contact with new sites have come: in the past six months, over 35 “contact requests” have been made to sites that are part of Site-Finder as a result of their being on the platform.

Furthermore, we have received reports from sites stating other perceived benefits of being a part of Site-Finder, including receiving monthly news about global grant and funding opportunities, and making use of the other resources across the Global Health Network. For example, one site commented: “I particularly used the [research ethics eLearning] course for my MSc students very successfully. In addition we have been in contact with a

number of sites on possible collaboration for a number of activities”; another commented, “I have benefited a lot from the posting of the grant calls.”

Discussion

The feedback related to Site-Finder has been encouraging, with sites responding positively to the concept and need for this tool. Following Site-Finder’s launch, the collaborative aim is that registered research sites will partner on more diverse research projects identified through Site-Finder and that this diversification will then allow sites greater sustainability and stability for staff with long-term broad training. We hope this will lead to a community of research sites with strong experience of conducting high-quality studies. These sites will then have the breadth of experience and independent capacity to initiate their own studies and engage in local research.

Situating Site-Finder within the Global Health Network, an existing, widely used community of researchers working in global health, provides distinct advantages. A single sign-on across the entire network means that one Site-Finder registration opens a further wealth of information to users who wish to further develop research skills and initiate their own studies. Such resources include regulatory information, guidance articles, downloadable tools and templates, eLearning courses, a Professional Membership Scheme to track continued professional development, and expert-moderated discussion forums (see Figure 2).

The Global Health Network aims to accelerate and streamline research through an innovative digital platform, facilitating collaboration and resource sharing in global health, and has attracted over 200,000 visits to date.

The Global Health Network is also keen to encourage sites to use Site-Finder in other ways, for example, by finding other local sites for shared training days, facilities, local research studies, or organised staff exchanges. Some localised and administrative support will be offered if sites want to participate in these activities.

The team will also be investigating ways of using Site-Finder to increase locally led research, for example, helping users of Site-Finder to access the other resources available on the Global Health Network for activities such as protocol writing, training staff, and reporting their work. One ongoing challenge faced by Site-Finder is whether it can support and encourage more locally relevant research

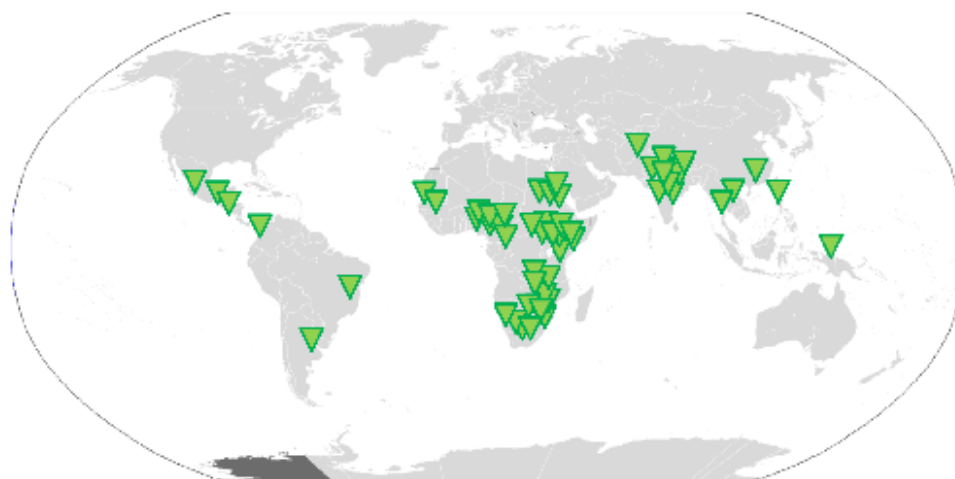


Figure 1. Map showing the distribution of 110 research sites as of July 2014.
doi:10.1371/journal.pntd.0003225.g001

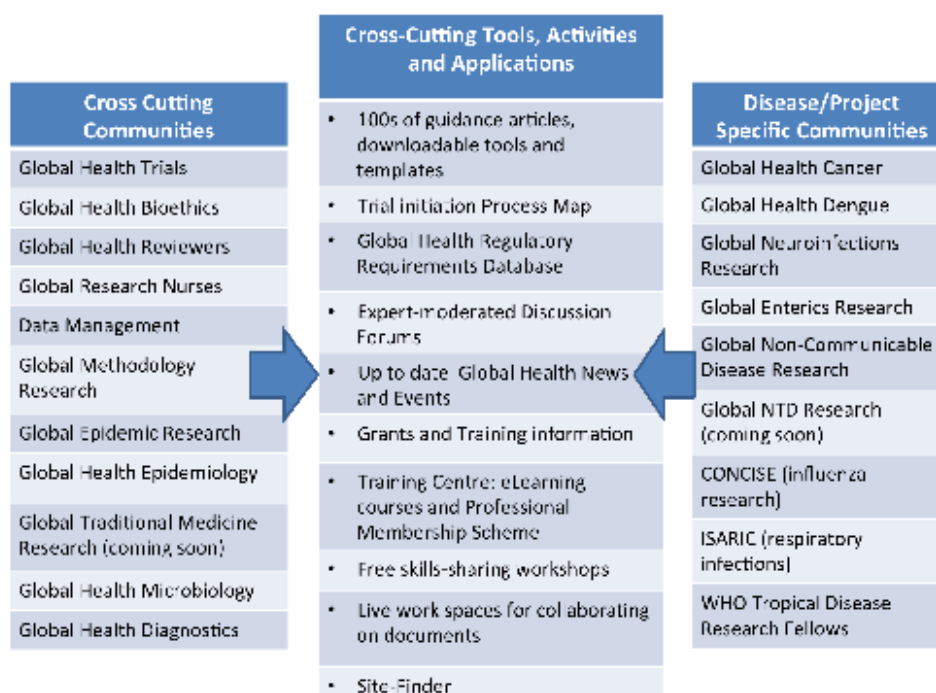


Figure 2. Applications and communities within the Global Health Network.
doi:10.1371/journal.pntd.0003225.g002

or whether it will exacerbate the trend of encouraging studies mainly relevant to high-income locations [5]. So far, all the studies entered have been from noncommercial organisations or universities and relate mainly to relevant diseases, including NTDs, maternal health, HIV, and TB.

This concern was also discussed in detail within the working group that developed Site-Finder, and it was agreed that Site-Finder should allow commercial research opportunities to be posted because there is much value in facilitating different types of research at sites. The experience, funding, and training opportunities that arise from taking part in industry and other regulatory-type clinical trials are of enormous value to the sites involved. Furthermore, it is up to the sites themselves and the countries to decide who they collaborate with and what types of trials they wish to take part in. The objective of Site-Finder is to increase opportunities for researchers and their study teams. Working on a variety of study types will benefit sites by diversifying

and overlapping funding streams, thereby keeping funding long-term and consistent, allowing for the development of infrastructure and a robust team of research staff who have experience in varied types of studies and in different disease areas.

Site-Finder will be continually assessed to ascertain whether it is working successfully—that is, linking research sites with sponsors and collaborators. Analytics data will be used to show the numbers of visitors from each location who have accessed the site and the information that they are accessing. Short semiannual questionnaires will be sent to the sites and collaborators to assess contact between Site-Finder users and to gain information on whether the research sites are also carrying out locally led research.

Conclusions

It is important that researchers and sites are supported in developing comprehensive and sustainable research skills that enable the initiation of locally devised and

locally led research studies. This requires access to guidance, tools, and resources for thorough training and support [10]. Diversifying research performed at sites will help to equip staff with the confidence and skills to initiate research into local health issues, therefore helping to create evidence to alleviate local disease burdens, particularly in neglected tropical diseases [10]. Site-Finder has been built, evaluated, and launched to enable research sites to engage in multiple and diverse research collaborations and thus strengthen their capacity. Because it is situated within the infrastructure of the Global Health Network, Site-Finder also allows sites to build their skills and knowledge by accessing the information and peer support that is abundant on the Network.

Although at an early stage, initial feedback on Site-Finder is highly positive. This indicates that the web application will successfully link research sites and new projects and succeed in the goal of increasing equity in access to research opportunities.

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NEWS

Website pools clinical trial forms for use in developing countries

Healthcare advances in low-income countries are chronically hampered by a lack of locally run clinical trials. To wit: a whopping 80,771 clinical trials have been registered in the US since 1999, compared with only 216 in Bangladesh and 93 in Nigeria over the same time period, according to a database maintained by the World Health Organization. Although the movement of some commercial drug trials to resource-poor countries has sparked ethical concerns, global health advocates are clear in their assertion that more locally initiated research trials in those countries would benefit developing world populations.

Now, a new online resource scheduled to launch on 8 July aims to help by providing a trial initiation ‘process map’: an interactive flow chart that summarizes all the various stages of a clinical trial and links to guidance articles to assist local researchers in setting up new studies. It is part of the Global Health Trials website of the Global Health Network, a collection of online research forums that has received \$5 million in funding from the Seattle-based Bill & Melinda Gates Foundation since 2010.

According to Trudie Lang, who heads the Oxford-based Global Health Trials site, “People find it difficult to find out the basics of how to run a study, so the process map gives a route map with all the steps.” The new flow chart provides a generic guide to all aspects of running a trial, from developing research questions to beginning patient recruitment. It provides information relevant to all countries, diseases and types of studies. “It doesn’t really matter whether you are working on a malaria study in Kenya or a visceral leishmaniasis study in Nepal,” Lang explains, “there are still things that you do that are the same.”

At each trial step, the flow chart provides links to relevant examples of standard documents and templates. These documents, many already available on the Global Health Trials website (<http://globalhealthtrials.tghn.org/>), have been donated from researchers in Europe and the developing world so that they can be adapted for use by other developing world researchers. Lang says that of the templates presently on the



Due process: New website provides an interactive flow to guide clinical researchers in the developing world.

website, the most accessed documents are examples of informed consent forms and standard laboratory operating procedures. Without specific training, consent forms are particularly difficult to create, owing to complicated legal requirements as well as requirements from trial sponsors.

Users will also be able to ask questions and post advice to others through a users’ forum. Once contributions reach a critical mass, Lang plans to implement an Amazon.com-style users’ ranking system, to allow the most popular contributions to be listed first.

Forum for change

According to Elizabeth Allen, a clinical research manager from the University of Cape Town in South Africa, additional benefits lie in the local context that the online flow chart can provide through the users’ forum. Allen runs antimalarial efficacy trials in Mozambique, South Africa and Swaziland, and she has set up a South African members’ network on the Global Health Trials website. Using the new flow chart users’ forum, she plans to share her own local information with

the whole community, such as information on South African trial registration requirements in addition to standard general requirements. Allen says that many of the problems are practical issues, for example, “it’s knowing the tips on how to complete a trial application so it will be successful in terms of its regulatory review.”

Since 2010, 183,000 users have visited the Global Health Trials site, with 80% coming from low- and middle-income countries, with the largest proportion of users being from Africa. Lang says she does not have a specific target for the number of users but thinks the site is on track to reach 1 million visits within three years.

Haleema Shakur, a trial design expert who co-directs the Clinical Trials Unit at the London School of Hygiene & Tropical Medicine, is supportive of the site’s information-sharing aims but feels that capacity building needs training through direct mentoring. Shakur says that at the moment there is a “chicken and egg situation,” with funders unwilling to fund inexperienced staff who subsequently lack opportunities to gain training. “Unless funding bodies are willing to invest in developing units within countries,” she says, “I don’t know if you are ever going to change the situation.”

Rachel Brazil

“The new flow chart provides a generic guide to all aspects of running a trial.”

END
