Study title

Strategies for developing sustainable health research capacity in Low and Middle Income Countries; a prospective, qualitative, multi-site study investigating the barriers and enablers to locally-led clinical trial conduct in Ethiopia, Cameroon, and Sri Lanka

Study supporting material document: **Methodological approach**

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Methodology

1.1 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” [1]. 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 [2]. 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 [1 2].

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 [3-7] and other authors [8-10]. 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. [11]. Further consideration of this is presented in "Strengths and limitations of the study design" (section 1.12,).

Although evidence-based practice provides a theoretical framework within which to approach problems by identifying evidence gaps and answer priority questions [12], 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 [13]. 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 [14] . 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" [13]. 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 [15].

In addition to Robson's book on "Real World Research" [13], 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 [8 16-18], 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 [19-21]. Therefore, the issues at the individual level were given greater attention in this thesis. Additional influential literature included: being systematic [22], using organisational development approaches [23], and the importance of developing conceptual frameworks [16]. 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.

1.2 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 [24] and is broadly in-line with *generative causation* used in Realist research to understand phenomenon as they happen in the field [13].

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 [8]. 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" [25],* and developing potential frameworks to measure health research capacity development [26]. 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 [25].

Importantly, both Yin's perspective on case studies [24] and Realist perspectives [13] 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" [24].* 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 [24].

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 [27-29].

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.

1.3 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.

1.3.1 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 [30]). 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.

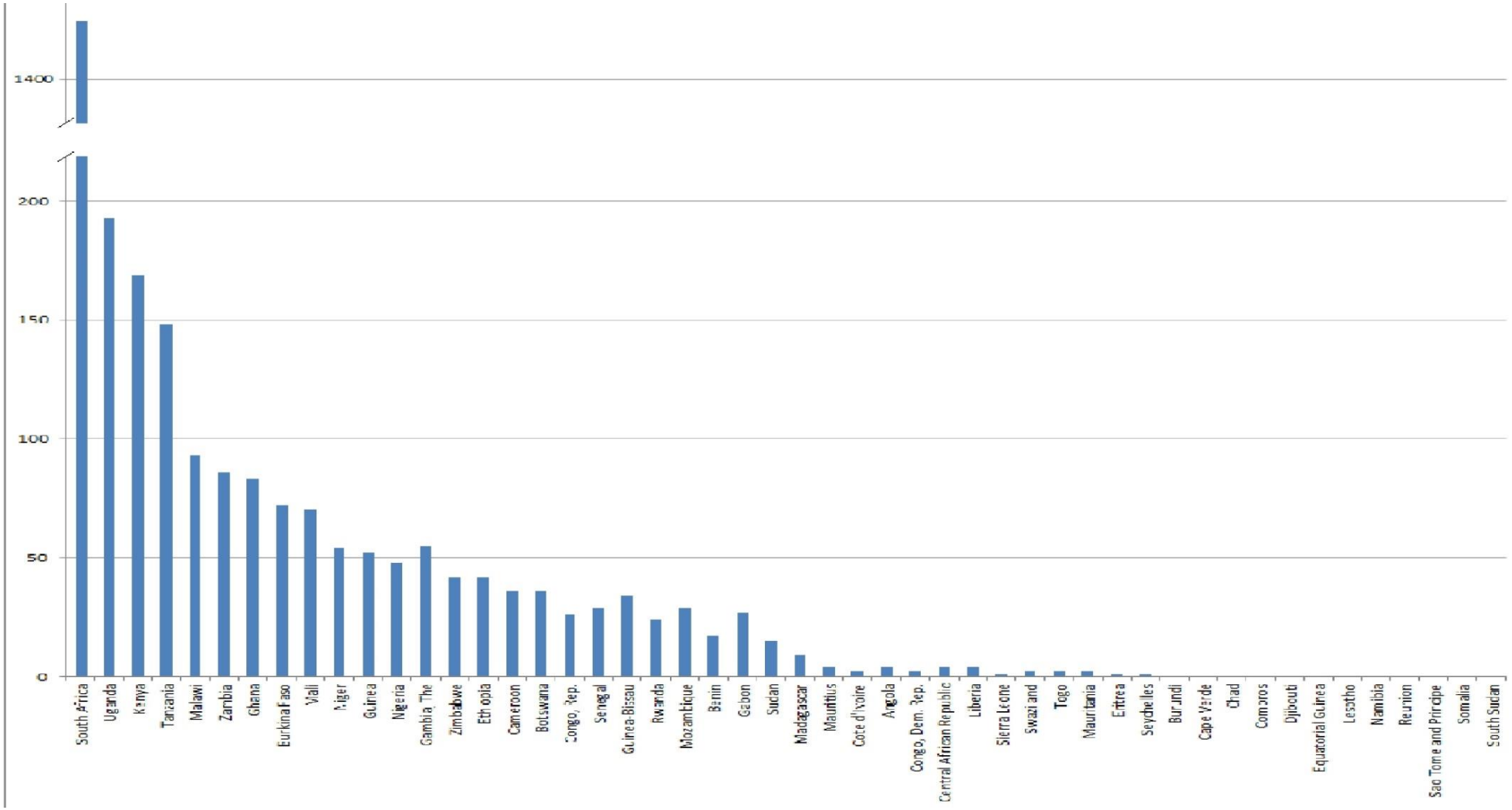

Figure 0-1 Number of clinical trials registered on WHO International Clinical Trials Registry Platform [30] on 10/09/12 by country of recruitment for Sub-Saharan Africa

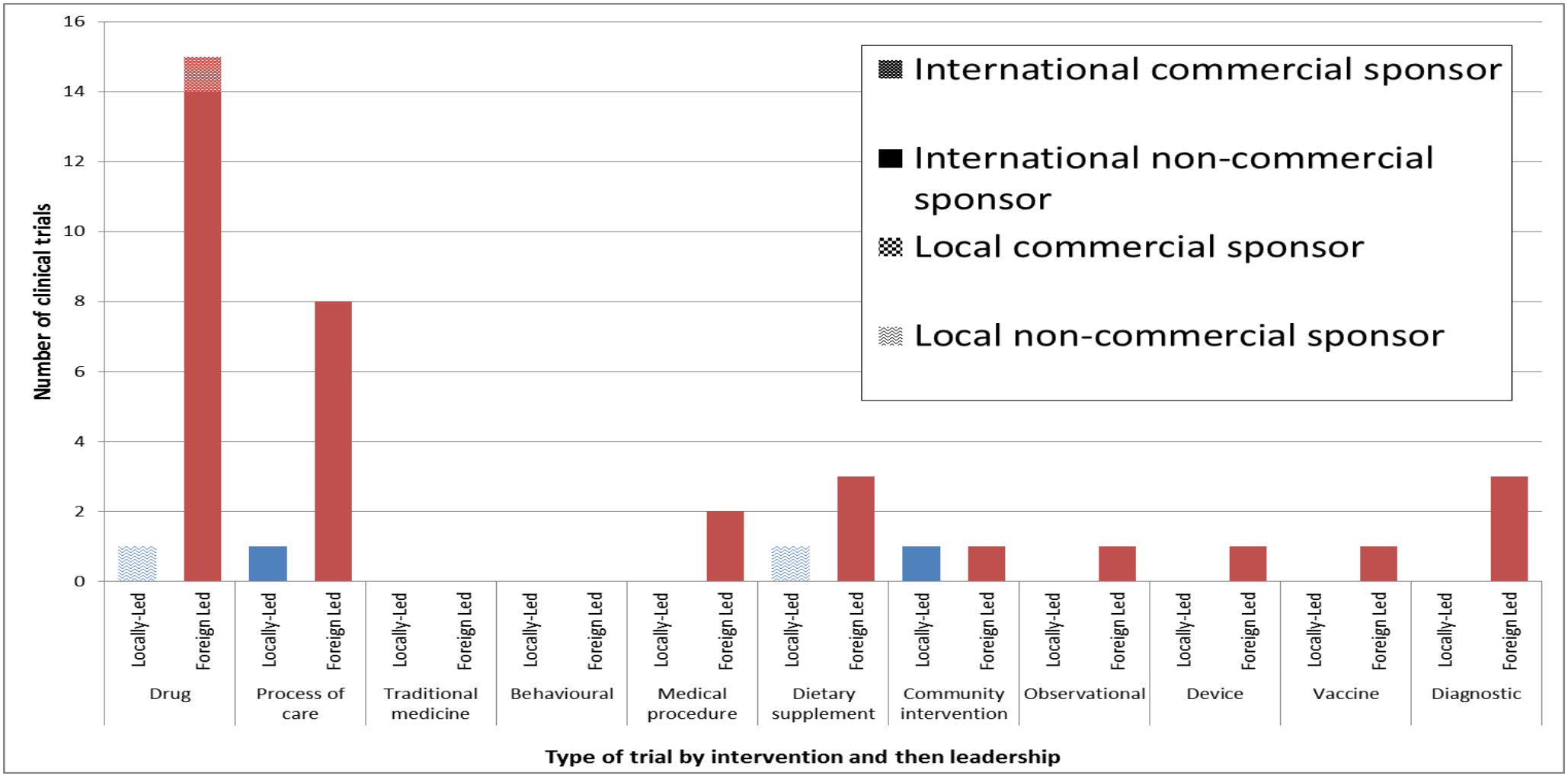

Figure 0-2 Number of unique clinical trials in Ethiopia by type of trial intervention, leadership and sponsorship type;

as registered on the WHO International Clinical Trials Registry Platform [30]. Data correct of at time of field work (March 2011)

1.3.2 Cameroon

The second case-study was a full-scale study informed by the theoretical framework and research experiences developed though 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 [30]. 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 0-1 Comparison of development indicators for Ethiopia and Cameroon

Source: World Bank (access date 10th March 2014) [31]

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)

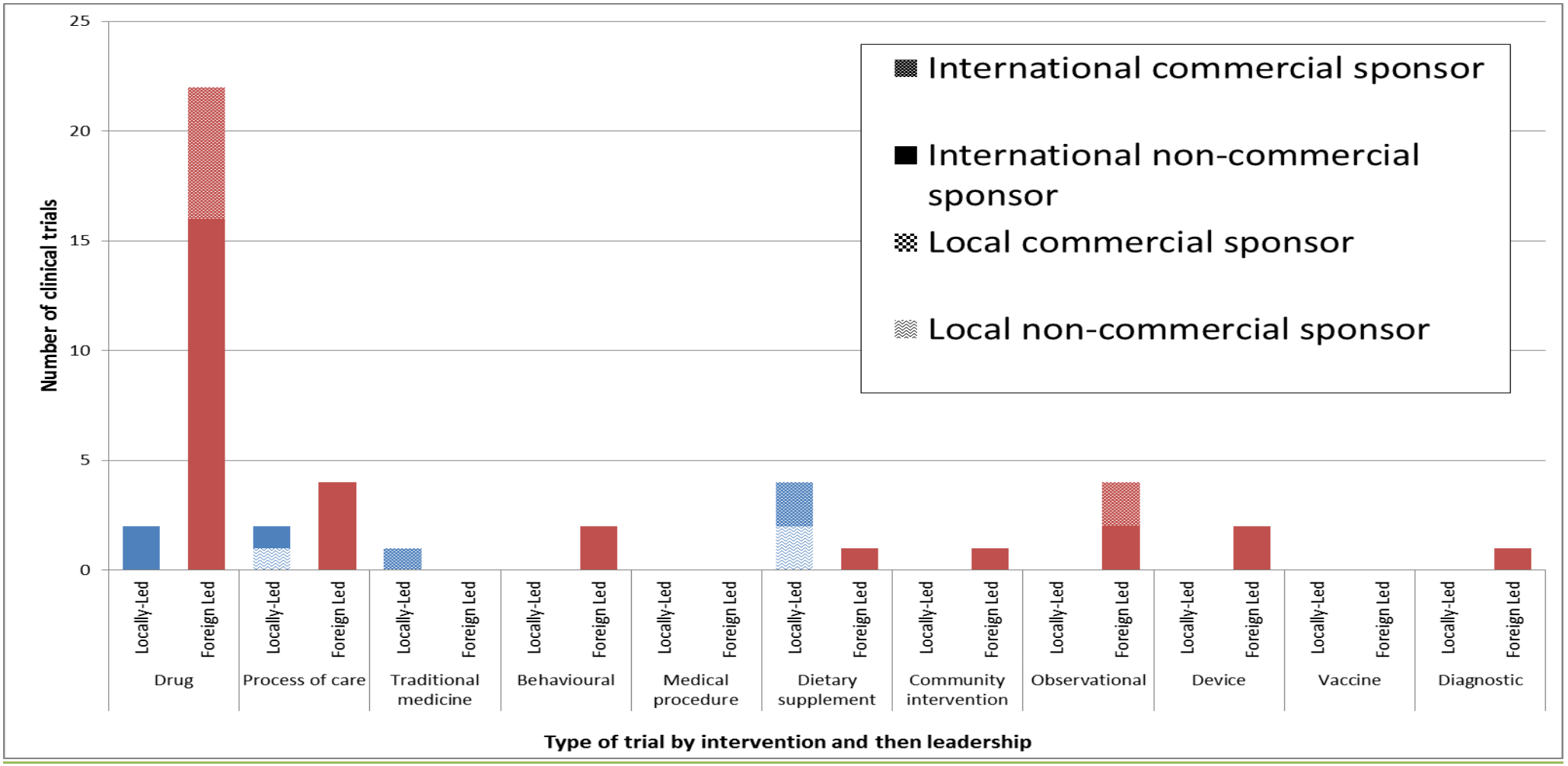

Figure 0-3 Number of unique clinical trials in Cameroon by type of trial intervention, leadership and sponsorship type;

as registered on the WHO International Clinical Trials Registry Platform [30]. Data correct of at time of field work (July 2012)

1.3.3 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 [32]. 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, [30]) 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 [32]. 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.

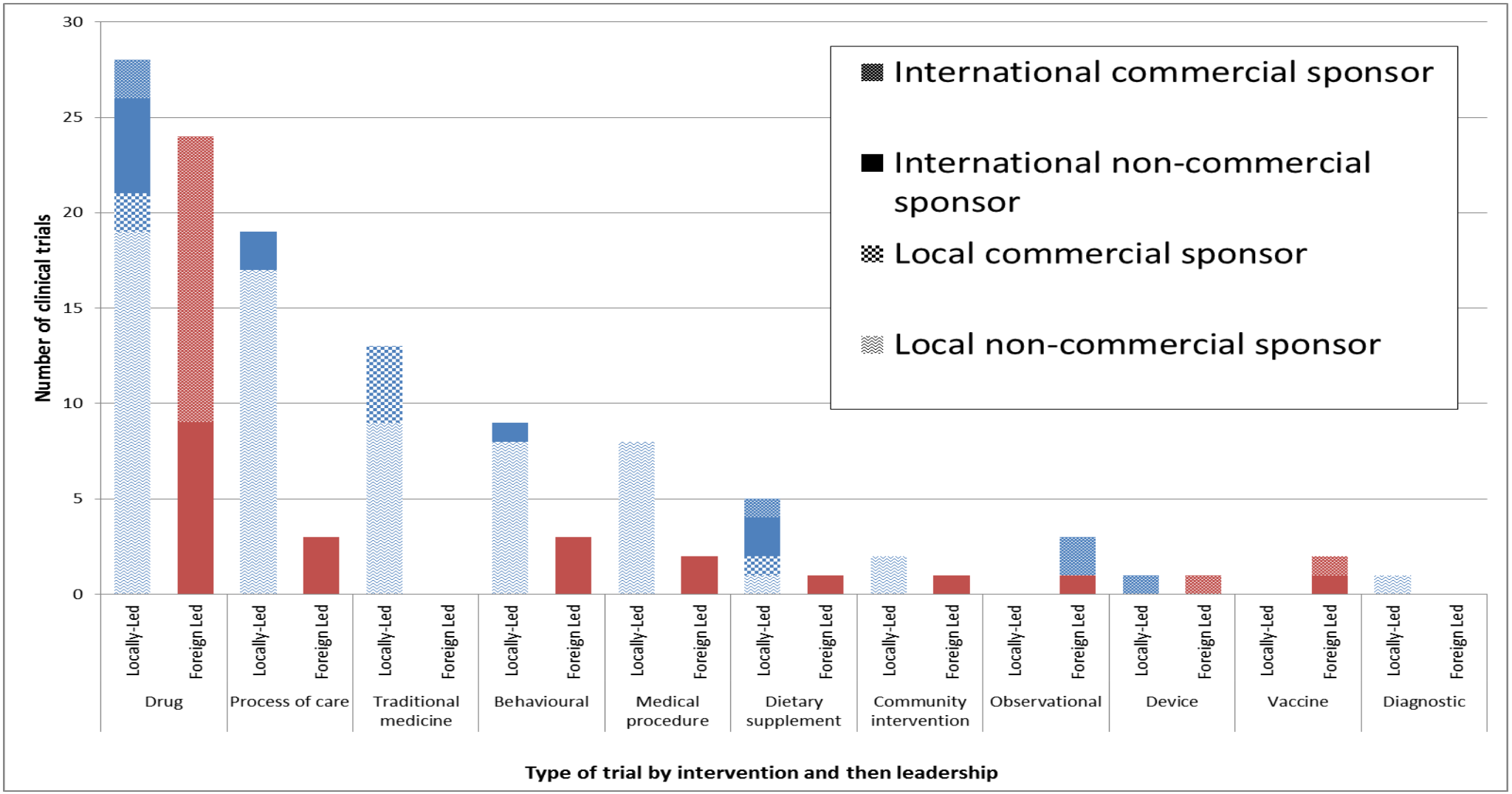

Figure 0-4 Number of unique clinical trials in Sri Lanka by type of trial intervention, leadership and sponsorship type;

as registered on the WHO International Clinical Trials Registry Platform [30]. Data correct of at time of field work (February 2013)

Table 0-2 Comparison of development indicators for Ethiopia, Cameroon and Sri Lanka

Source: World Bank (access date 10th March 2014) [31]

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)

1.4 Study population and selection criteria

There is a lack of consensus on monitoring indicators for research capacity development [10 33], and few accepted frameworks for evaluation [16]. 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 [34] and there must be greater inclusion of those who directly experience issues [35]. 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 [8]. Therefore recruiting research actors "who grapple with the issues on the ground" [36] 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.

1.5 Choice of methods

Within Global Health there has been increasing pressure to employ qualitative research methods [37] and this has been extended to examining the processes of clinical trial implementation [38] and research capacity strengthening initiatives [10]. 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

[37]. 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 [39] or contextual drivers of failure [40]. 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.

1.5.1 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 [41]. 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.

1.5.2 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 [13].

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.

1.5.3 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 [42].

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 [43]. 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 [42].

1.6 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.

1.7 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.

1.8 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.

1.8.1 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 1.10).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.

1.8.2 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.

1.9 Procedures specific to research exercises

1.9.1 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 Protocol.

1.9.2 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.

1.9.3 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.

1.9.4 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.

1.10 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 [44]. 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 [44], where guiding literature and established explanatory models are scarce and it is not known if they would be relevant to the phenomenon being studied [13]. It is sometimes criticised as being largely descriptive, rather than interpretive. However, this is usually when the

focus of analysis is too broad [13] or analysis is limited to only labelling content rather than interpreting deeper meanings [44], particularly explaining phenomenon by developing conceptual frameworks or models [13].

As such, approaches and practices of thematic coding analysis can vary, especially in the level of depth and interpretation [13 41]. The approach used in this study followed guidance by Green and Thorogood in their book on "Qualitative methods in healthcare" [44]. 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 [44] (a scientific observers "culturally neutral" account of the respondents behaviour or belief which can potentially be understood across cultures [44]). 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 [44]. 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, 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 (1.12).

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 0-1 The five iterative stages of thematic coding analysis.

Adapted from Green and Thorogood [44]

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.

1.11 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 1.7.

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.

1.12 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 [25]. 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.

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 [24]. 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 [25]. Furthermore, although there are warnings that pooling data to form a holistic case can lead to shallow and abstract findings [24], 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 [45]. 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 [45 46]. 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.

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 [13]. 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" [37]. Failure to appreciate these epistemological differences leads to "a clash of knowledge paradigms" [37].

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 [13]. 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 [37], and a thorough understanding and enactment of "best" qualitative research practices [38]. There are a number of different interpretations of what defines rigorous and "best practice" qualitative research [38], but one key hallmark is building "trustworthiness" by being transparent about the research processes leading to the interpretation of the findings [37]. Guidelines to achieve this have been produced [47] 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 [48]. 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 [46]. 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 [48].

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