

## 1.1 Study title

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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: Introduction to the study**

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*“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 <sup>1</sup>*

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## **Introduction and the research question**

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### **1.2 Justification for the research**

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#### **1.2.1 The need for health research in LAMICS**

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Low and Middle Income Countries (LAMICs) disproportionately suffer the greatest burden of disease globally <sup>1</sup>. At the turn of the millennium LAMICs accounted for 85% of the world’s population but 92% of the global disease burden <sup>2</sup>. To improve their health and development status, it was <sup>1</sup>, and still is <sup>3</sup>, 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 <sup>4</sup>. This proposal partly arises from ethical concerns over the potential risks and benefits for local stakeholders <sup>5</sup> but also because research evidence produced in one setting may not be directly applicable to other contexts <sup>6</sup>. This may be due to differences in disease profile, population genetics, environmental conditions, behavioural and cultural factors and resource availability <sup>7 8</sup>. Externally generated evidence is often treated with caution by policymakers delaying its adoption into clinical practice and limiting its usefulness for

policy and practice <sup>9-11</sup>. 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” <sup>7</sup>.

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 <sup>1 3</sup>, which is now known as the 10/90 gap <sup>2</sup>. 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 <sup>8 12 13</sup>. 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” <sup>1</sup>. This marked the beginning of a “revolution” in health research <sup>8</sup> where there was a surge of investment and concerted effort to conduct health research aimed at solving health problems in LAMICs <sup>2</sup>.

### **1.2.2 Progress in health research in LAMICs**

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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 <sup>3 [15][16]</sup>. Although causality cannot be assigned due to lack of monitoring data <sup>14</sup>, this improvement is attributed to a variety of mechanisms, including foreign investment <sup>8</sup>, a revised strategic focus at the international level <sup>15</sup>, and international research collaborations and networks between High Income Country (HIC) research organisations and LAMIC researchers <sup>16-18</sup>. HIC involvement in LAMIC

health research<sup>3 13 19</sup> 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<sup>3</sup>. Furthermore most of the research conducted in LAMICs was led by High Income Countries (HICs)<sup>17 20</sup>, and despite some improvements, many LAMICs still lack capacity to self-sufficiently undertake research<sup>3</sup> and translate findings into policy<sup>17 21</sup>. As such, development of LAMIC nation's capacity to address their own health problems appears enduringly problematic, despite years of international collaborations and investment<sup>3</sup>. Therefore these gains in health research, in most circumstances, do not appear sustainable without continued strong foreign support<sup>12 22</sup>, which is itself questionable in light of recent austerity reducing international development assistance<sup>3 23</sup>.

Part of the blame for this is broadly attributed to LAMIC governments failing to take responsibility for national health research<sup>12 22</sup> and therefore not prioritising and investing in research, despite often growing economies<sup>3 23</sup>. This perpetuates inadequate local research capacity in terms of: stewardship and governance<sup>4 10 24</sup>; human<sup>25-27</sup> and material resources<sup>25 28</sup>; research support<sup>12 28</sup>; knowledge resources<sup>26 28</sup> and infrastructure<sup>29</sup>; and translation of research into policy and practice<sup>25 30-32</sup>. These capacity constraints then introduce barriers that inhibit research generation<sup>10</sup> and make local researchers dependent on foreign collaborations<sup>33</sup>. 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<sup>1</sup>,

*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<sup>8 34</sup>. Accordingly they often bypassed local institutions by setting up parallel structures<sup>5 35</sup> and failed to adequately include local researchers and stakeholders in research conduct<sup>5 35</sup> which prevents the possibility of local capacity development<sup>23 34 36 37</sup>. 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<sup>17</sup>. Finally, this externally driven approach<sup>24</sup> where research was essentially done for or on LAMICs, rather than with or by them<sup>38</sup> was also argued to obstruct nation states' ability to assume responsibility for research<sup>31 38</sup>. This is because it took initiative and involvement away from local stakeholders<sup>38</sup>. 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.**

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

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 <sup>14 31 40 45 47-49</sup>. However, these suggestions have been presented since the millennium, and little appears to have changed given that HICs still dominate LAMIC research <sup>44 50 51</sup> 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 <sup>3</sup>. This suggests that 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 <sup>3</sup>.

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

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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 <sup>47</sup>. This is because experts suggest that for capacity

development to be successful, tailoring of capacity development to the specific context<sup>24 52</sup> and goals of the development activity is needed<sup>47</sup>. To be able to choose the most appropriate interventions for a given context, information on the contexts where the recommendations came from<sup>30</sup>, and the context where capacity development is to be delivered is needed<sup>24 52</sup>. 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<sup>28 31 53</sup>.

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<sup>24 52</sup> or health research capacity development strategies<sup>30</sup>. This paucity of empirical evidence for informing development strategies was identified by both authors<sup>54 55</sup> and the *chapter 2 literature synthesis*. This is problematic given the opinion that development recommendations should be based on situated empirical evidence<sup>17 24 51 52</sup>. This all suggests that to develop sustainable local research capacity, more situational analyses<sup>24 52</sup> and empirical research on the strengths and weaknesses of national health research systems<sup>3</sup> and how to develop them are needed<sup>54 55</sup>. 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

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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<sup>8</sup>. 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<sup>3 36 56</sup>. As such they are considered very important for establishing the efficacy and safety of new interventions<sup>36 56</sup>, informing systematic reviews that are increasingly promoted to guide clinical decision making around the world<sup>3 6</sup>, and providing convincing evidence to influence public health policy<sup>4 57 58</sup>. 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<sup>3</sup>.

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.”<sup>59</sup>. 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<sup>60</sup>.

Given the need for more high-quality<sup>8</sup> context -specific data for local decision-making<sup>61</sup>, 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<sup>37 41 62 63</sup>. 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<sup>49</sup>. However, like other types of health research, despite the increasing conduct of internationally-led clinical trials in LAMICs<sup>9</sup>, development of self-sufficient trial capacity has proved elusive; clinical trial capacity remains limited<sup>9 34 41 63 64</sup>, too few clinical trials are conducted<sup>34 64</sup>, and most trials are still foreign-led<sup>9 55</sup>. 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<sup>3</sup>. However, the World Health Report points out that the difficulty of clinical trials varies according to the intervention studied<sup>3</sup>. Disease management<sup>36</sup> and implementation trials<sup>3 65</sup> are likely to require less resources than novel therapeutic trials, and are therefore potentially more feasible for LAMICs to address self-sufficiently<sup>3 36 41</sup>. 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 <sup>2 7 9 45 65</sup>, foreign-led trials usually only investigate novel interventions <sup>23 41</sup>.

Despite the recognised importance of locally-led clinical trials for contributing towards more self-sufficient LAMIC health research capacity <sup>9 36 41 55 63</sup> and their comparative operational difficulty compared to other research methods <sup>3</sup>, the chapter 2 literature synthesis and other authors <sup>37 63</sup> 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 <sup>17</sup>, rather than capacity to lead their own <sup>37 63</sup>, 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 <sup>62</sup>. This is particularly problematic because although locally-led trials are reported to face similar challenges as internationally-led studies <sup>62</sup>, 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 <sup>63 66 67</sup>.

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

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#### **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

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