Bridging the gap: aligning research efforts with disparities in burden of disease - experiences of early-career researcher conducting investigator-initiated trial in a low-income country

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Background: Randomised controlled trial (RCT) is an empiric investigation in which the objective is to elucidate cause-and-effect relationships when it is feasible to impose the procedures or treatments whose effects it is desired to discover**.** High-income countries have been at the forefront of development and innovation in the conduct of randomised controlled trials (RCTs). More than 80% of RCTs listed on ClinicalTrials.gov are conducted in the developed world. A 2018 study revealed a staggering difference in clinical trial sites; approximately 83% of trials had been conducted in 25 high-income countries, whereas <5% had been conducted in 91 middle or low-income countries. Some of the trials being conducted in developing countries seek to answer questions of the developed world. Diseases of relevance to high-income countries are investigated in clinical trials seven to eight times more often than diseases whose burden lies mainly in low-income and middle-income countries. Low-income countries bear nearly 90% of the worldwide burden of disease yet there is a disturbing underrepresentation of research addressing this inequality. Lack of research skills exacerbate the problem. It is in these poorest regions where research-led solutions could bring the greatest impact on health outcomes. To address the lack of representation of RCT research in low-income countries, the ideal would be for local investigators to lead the initiation and conduct of locally relevant trials, as they will be more responsive to local population health needs, disease burden, national priorities and infrastructural challenges. While there are calls supportive of locally driven research, local investigators initiating RCTs in low-income countries encounter many barriers, preventing RCT execution. We provide a discussion on infrastructural, financial and other resource-related opportunities and key challenges encountered and conclude with lessons learned and propose the way forward.

Aim: To use our investigator self-initiated trial on mobile phone text messaging plus motivational interviewing in promotion of breastfeeding among women living with HIV in South Africa and provide some of the early-career investigator experiences, in setting up and executing a trial in a low-income country.

Study type and setting: We are conducting a RCT to determine the effect of text messaging plus motivational interviewing on sustaining breastfeeding, among 275 women living with HIV and their infants. Study recruitment started end of July 2022 at Khayelitsha district hospital. We randomly assign study interventions within 24 hours of giving birth, for 24 weeks. Participants have in-person follow-up study visits at weeks 2, 6, 10, and 24 post randomisation at Masiphuhlisane research centre. Intervention facilitator administer the study intervention. Research counsellors administer a baseline questionnaire and follow-up study questionnaires.

Financial issues: We first conducted a pilot trial to test the feasibility of the current large trial, with a budget of R350 000 (~US$22000) for the pilot trial. We submitted multiple grant applications for the pilot trial and secured enough funds within three years. The successful grant applications were those submitted to Stellenbosch University, ranging between R15 000 and R150 000. Recruitment for the pilot trial was delayed due to insufficient funds, subsequently, some of the awarded funds (R50 000) were returned due to grant conditions which required awarded funds to be spent within a stipulated timeframe. The pilot trial capitalized on the established research infrastructure at FAMCRU, including office space, human resource services, and transport services, at no or subsidized financial cost. In 2020, we secured the EDCTP Grant to run the large trial. We could not access FAMCRU infrastructural support and human resources services as initially planned. Subsequently, we made several changes to implementation of the large trial which negatively affected the study budget. We successfully applied for top up funding of more than R600 000.

Facilities and other resources

Ethics clearance: We were exempted from ethics document processing fee for the pilot trial because it was solely funded by Stellenbosch university. For the large trial, we applied for ethics clearance before the start of EDCTP action period because of the tight funding time frames. We secured funds elsewhere to cover ethics document processing fee for the large trial. Both the pilot trial and large trial received ethics clearance within three months.

Western Cape Government, Department of Health (WCDH): Application to the WCDH requesting permission to access the healthcare facilities for study recruitment. The WCDH has a National Health Research Database that assist researchers with applications submission for review by the Provincial Health Research Committee granting access to provincial healthcare facilities. WCDH approved each study within six months. Our application of the large trial to the WCDH was during the COVID-19 pandemic, when review of non-COVID-19 research was not prioritised. We successfully requested the WCDH to review our study because of the tight funding timeframe. We also requested the WCDH approval before the EDCTP action period to meet the funding timeframe. Getting ethics and WCDH approvals for large trial took nine months. For the pilot trial, due to lack of space for research in healthcare facilities serving a large pool of eligible participants, we were granted access to recruit from a rural healthcare facility, serving a small number of our target population which prolonged recruitment period. For the large trial we managed to negotiate research space at Khayelitsha district hospital, serving a large pool of our target population.

Other: We use Research Electronic Data Capture (REDCap), a web-based application to capture data at no cost, because Stellenbosch University is a REDCap consortium partner. The Stellenbosch University grant management office assist with the monitoring of expenditures against approved grant budgets.

Lessons Learned and way forward

- An enabling environment for clinical research improved efficiency of the planning and execution of trials.
- It is prohibitively expensive to establish research infrastructure. Leveraging on existing research infrastructure, and linking with established research networks, may optimize use of available research resources and promote knowledge transfer.
- Tight funding timeframe is a barrier. Relaxing funding timeframe may benefit investigators in low-income countries who require an extended period to secure enough funds to start a research project.
- Collaboration and co-ownership of research with stakeholders in routine health services facilitates access to healthcare facilities for research.
- Feasibility studies are useful in identifying potential challenges that may be encountered in the conduct of large definitive trials.