In global health research, short-term, small-scale clinical trials with fixed, two-arm trial designs that generally do not allow for major changes throughout the trial are the most common study design. Building on the introductory paper of this Series, this paper discusses data-driven approaches to clinical trial research across several adaptive trial designs, as well as the master protocol framework that can help to harmonise clinical trial research efforts in global health research. We provide a general framework for more efficient trial research, and we discuss the importance of considering different study designs in the planning stage with statistical simulations. We conclude this second Series paper by discussing the methodological and operational complexity of adaptive trial designs and master protocols and the current funding challenges that could limit uptake of these approaches in global health research.

Introduction

Randomised clinical trials are an underused tool in global health research that have the potential to drive evidence-informed policy making in low-income and middle-income countries (LMICs). Panel 1 shows the findings of systematic searches of trials from two key areas of global health: maternal, newborn, and child health, and malaria. Most global health trials have a simple fixed design that uses two arms, is typically small in sample size (less than 100 patients), and is underpowered. Although many trials have been undertaken in these research areas, the information derived from these trials is inconsistent and might suggest the need for both better trial planning and coordination.

Newer approaches for the planning and implementation of trials than these fixed, two-arm designs are currently being used by specialised trialist groups that are largely based in (and working in) the USA and the UK. Alternative design choices include data-driven approaches in clinical trial research that are known as adaptive trial designs. An adaptive trial design is a type of trial design that allows for prespecified adaptations throughout the trial, in which the decision to adapt is dependent on the interim data collected.5,6 Particularly when epidemiology is poorly understood and sample size calculations are challenging, this type of trial can minimise the limitations conferred by fixed trial designs by planning for possible changes and methods of evaluating interim data through extensive simulations.7,8 Because there are many unknowns and difficulties in trial planning in LMICs, simulations can be a powerful tool that can enable more efficient and ethical clinical trial research for global health research.5 Simulations can help to avoid trial design decisions that trial investigators might later regret, after the trial shows negative findings (areas of anticipated regret).1 Whether the design is adaptive or not, simulations can be used for any designs and any clinical areas of research, but they are not often used in the context of global health.9

Adopting the framework of master protocols (which have also been referred to as core protocols) might help to minimise the fragmented nature of research efforts within the global health trial landscape. The term master protocol generally refers to a single overarching protocol that has been developed to evaluate multiple interventions, with a general goal of improving efficiency and standardisation in clinical research.10–14 Compared with conventional clinical trials, master protocols are planned to be larger in scale and offer flexibility and sustainability in answering multiple research questions over longer periods of time under a single protocol.10,15 A landscape analysis of master

Key messages

- An adaptive trial design is a validated method that has been used extensively but, in the past 30 years, this approach has predominantly been used for pharmaceutical therapeutic research under regulatory scrutiny in high-income countries. Consideration of data-driven approaches might become increasingly important for global health trial investigators working in low-income and middle-income countries.
- No trial designs should be used by default. Instead, trial planning practices should include considerations of multiple designs and the possibility of using statistical simulations to inform efficient trial designs for the given clinical question in conjunction with other factors.
- The principles of master protocols and their subtypes in basket, umbrella, and platform trials can be tailored and adapted to suit the needs of a multitude of health problems. Such study designs might not only improve the quality and standardisation of trial research but could also help in reinforcing local infrastructure and improving training and professional development opportunities, particularly in low-income and middle-income countries, given that master protocol studies are generally planned to be large in scale and long term.
This Series paper builds on the discussion from the first paper of this Series. We first introduce the concepts of adaptive trial designs and master protocols, and we present specific study designs that can be applied in global health research. We discuss how the master protocol framework can be used to promote sustainability and holistically improve trial research in LMICs. We outline a general framework for improved trial planning and future considerations that both researchers and funding bodies can make to improve global health research.

**Adaptive trial designs for global health**

**Overview of adaptive trial designs**

In global health research, there are often many instances of substantial uncertainty regarding the natural history of the diseases and how best to intervene. As a result, assumptions with a high degree of uncertainty might be required, which can often be challenging to plan and design trials. Therefore, it is important to use clinical trial simulations to explore a multitude of scenarios to guide the selection of trial design parameters while considering different trial designs, to determine the optimal design for a given research question.

The default use of fixed trial designs can pose considerable inefficiencies that cannot easily be afforded in the context of constrained funding, as often applies to global health research. In clinical trials with fixed trial designs, the data are not typically evaluated until the last participant has finished their follow-up. Adaptive trial designs allow for more frequent learning by implementing preplanned interim evaluations that use prespecified decision rules. The ongoing learning nature of adaptive trial designs can test for the adequacy of the assumptions that the investigators have made going into the trial early, such that modifications to the trial designs can be made, to increase the likelihood of detecting a true-positive effect or stopping the trial early if the intervention is shown to be futile.

Although there might be potential concerns for investigator bias, adaptive trial designs are protocol-driven. The specific design components are not modified by the trial investigators. There are explicit plans for interim evaluations, potential adaptations, and decision rules that are written into the trial protocol before any participants are recruited into the trial. If any of the predetermined decision rules are met during an interim analysis, adaptations are made as planned, to avoid undermining the trial’s validity and integrity. Interim analyses are often done by independent statisticians and reviewed by an independent data monitoring committee. Data monitoring committees are often staffed by scientists and statisticians from HICs, but it is important for clinical trials set in LMICs to have representation of data monitoring committee members from the LMICs.

**Sample size re-estimation**

Sample size calculation is an important part of trial planning. Typically, little information is available with regard to baseline disease prevalence, anticipated dropout, loss to follow-up and other features essential for sample size calculations. As such, determining sample size calculations can be a difficult task; trial investigators in global health research undertake sample size calculations with assumptions that are justified with the use of a mixture of subjectivity, external studies with limited generalisability to the setting of interest, or small-scale pilot studies or proof-of-concept studies with high degrees of uncertainty. Sample size re-estimation can be a valuable tool for increasing the probability of detecting treatment effects. Sample size re-estimation is a type of adaptive trial design that allows for modification of the sample size target based on interim data. If the event rate is shown to be lower than foreseen at the interim analysis, the trial’s statistical power will consequently be lower than originally planned. Adaptive trials with...
planned sample size re-estimation would allow for the target sample size to be increased to improve the trial’s statistical power.

Seamless designs
For drug development, clinical trial investigations are usually done in phases, with earlier phases undertaken with exploratory purposes (eg, testing of dose ranges), followed by a confirmatory phase 3 trial that can provide strong evidence of drug efficacy or safety, or both.21 With conventional approaches to clinical trial evaluation, the knowledge from each phase can only be used after the trial is finished.22 Even if an early exploratory clinical trial is undertaken and shows results that are promising enough to justify a further confirmatory trial, clinical evaluation of such an intervention would be paused between the two clinical trials. However, a seamless design is a type of trial design that allows for a trial in the non-confirmatory stages to immediately continue onto the subsequent trial.23,24 The most commonly used seamless designs are seamless phase 2 to phase 3 trials, because phase 2 and phase 3 can have considerable overlaps in essential components (eg, clinical settings).24

Seamless designs can be useful for global health research. For vaccine development, as one example, the efficiency of trial investigation of candidate vaccines can be improved by use of the seamless phase 2 to phase 3 approach that has been used for a clinical evaluation of the 9-valent human papillomavirus vaccine by Joura and colleagues.25 Before this adaptive trial with a seamless design was undertaken, there was uncertainty about an optimal dose of the 9-valent human papillomavirus vaccine; therefore, this seamless trial began with a phase 2 stage that assessed three dosages (low, medium, and high) and immunological endpoints were used to select the optimal dosage for the subsequent phase 3 stage.26 The medium-dose vaccine, which showed adequate immunogenicity and safety profiles, was then seamlessly transitioned into a phase 3 trial, in which it was tested and confirmed for non-inferiority against the standard-of-care vaccine (4-valent human papillomavirus vaccine). The seamless design substantially shortened the amount of time to complete a conclusive phase 3 trial, given that there was no pause between phase 2 and phase 3.27,28

The nomenclature of different clinical trial phases developed under the drug development framework might not apply to all global health research. However, similar to early stage clinical trials for drug development, early stage exploratory trials evaluating non-pharmaceutical interventions in global health should be more concerned with false-negative discoveries. Because confirmatory trials require more resources than exploratory trials, undertaking exploratory trials before committing resources for confirmatory trials is important. Instead of undertaking exploratory and confirmatory trials separately, adopting seamless designs in which the exploratory stage can seamlessly continue onto the confirmatory stage (when positive findings are shown from the exploratory stage) could expedite clinical evaluations in global health research.

Response-adaptive randomisation (RAR)
RAR is a type of adaptive trial design in which allocation ratios can be adapted on the basis of interim analyses over the course of the trial.29,30 The allocation ratio is adapted to favour the allocation of future participants into the intervention arms with more favourable interim results.29,30 When a clinical trial investigation is done on potentially life-saving therapies for deadly illnesses, RAR can have a great appeal.29 For example, these type of adaptations might be important for candidate therapeutics to treat Ebola and COVID-19.29,30 Clinical trials with RAR can potentially minimise the number of participants assigned to control groups or other inferior arms.30 However, there are risks for bias and inefficiencies that might be introduced from having poorly planned RAR. These designs for two-arm trials will have lower statistical power than parallel-allocation designs (eg, 1:1 allocation). In multiarm trials, RAR can improve the probability of selecting the optimal treatment arm, given that allocation to the control is adequately maintained or even increased to match the allocation ratio of the best-performing intervention arm.31 To prevent bias that could arise due to poorly planned RAR algorithms, extensive rounds of simulations should be used to identify robust statistical constraints.31,32 It is also important to recognise the challenges of implementing RAR designs in resource-limited regions. For instance, obtaining informed consent is already a difficult task in global health research set in LMICs because many trials in these settings involve vulnerable populations, such as children. Given that these populations might have a varied understanding of research intent or conduct, RAR designs can raise complexities of obtaining consent from participants.33

Interim analyses for stopping trials early
Adopting interim analyses that allow for individual intervention arms or the trial itself to be stopped early can improve the ethics and efficiency of clinical trials for global health research. Interim evaluation in this context would involve generating performance metrics on the effectiveness and not just monitoring the trial progress from the data that are collected. Stopping a trial early could be due to superiority reasons, if the interim data show that the intervention has sufficient evidence to conclude that it is effective. For example, the HIV trial of male circumcision in South Africa (ANRS 1265) was ended early for superiority on the basis of an interim analysis undertaken when 63% of the total planned person-years had been observed.34 However, if the interim data show that a given intervention has inadequate benefit or sufficient activity, the trial can be

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stopped early for futility. In a 2020 large-scale HIV vaccine trial (HVTN 702) undertaken in South Africa, the independent data monitoring committee reported no benefits of the HIV vaccine when an interim analysis showed a similar number of infections in the vaccinated (n=129) and placebo (n=123) groups.41

Interim analyses for stopping trials early for either superiority or futility can improve the core ethical requirement of protecting research participants who deserve special considerations, such as child populations. Although it is commonly believed by researchers that individuals will enrol in clinical trials under the belief that their participation will help advance science,42 this is not often the case. Participants might agree to enrol in a clinical trial with a belief that they will gain personal benefit in return for their participation, because their participation could lead to access to clinical care and other benefits that they would not normally have, which is particularly likely in places where people have inadequate health-care access or care is of poor quality (which are contexts that are often targeted in global health research).43

Participants might be exposed to unknown risks given the experimental nature of clinical trial research, particularly in therapeutic interventional trials.44 Many clinical trials involve marginalised and vulnerable populations that might have a poor understanding of the research intent or conduct.45-47 This was the case for three early trials of pre-exposure prophylaxis for the prevention of HIV in Cambodia, Nigeria, and Cameroon, where ethical concerns for minimal engagement in care post-trial were cited as the primary reasons for stopping the studies early.48

There are several statistical methods for stopping trials early. There are group sequential designs that allow for trials to be stopped early if the test statistic, which corresponds to a p value, exceeds a specified boundary (a crucial value used to determine significance level) at a preplanned interim analysis.49 To ensure that the overall type I error rate does not exceed the desired α (eg, 5%), the stopping boundaries are usually set more stringently at the interim analyses. More stringent stopping boundaries are used at interim analyses to account for multiplicity (inflated errors due to multiple testing), to control for the overall type I error rate.50 Stopping rules under the Bayesian framework can also be implemented by prespecifying decision rules that are specified in terms of probabilities.51-53 For instance, an adaptive Bayesian trial might allow for the trial to be stopped early on the basis of superiority if the estimated probability of success exceeds a threshold; stopping trials early for futility can also be permitted if the estimated probability of success falls below a specific threshold. The thresholds for superiority and futility are usually determined with statistical simulations that yield desired operating characteristics.54

Other reasons for stopping trials early
In addition to superiority and futility reasons, there are other reasons to end trials early. Regardless of design, careful attention is required to monitor adverse events among participants during the trial, to allow for valid assessment of harm. If an intervention is shown to be harmful, early termination of the trial (or discontinuation of the intervention arm in multiarm trials) could occur. Measures to stop trials for adverse events are already commonly implemented in global health research. A trial might also end early if there are recruitment challenges that can prevent the trial from finishing in a timely manner. Recruitment is often a major challenge for clinical trials undertaken in LMICs.55-56 However, LMICs might not have similar recruitment challenges since there is often a higher burden of certain diseases.57-58 For low-prevalence diseases, such as neglected tropical diseases, it is important to consider whether it is feasible to recruit enough participants to answer the research question reliably in the geographical setting.

There might be external reasons for ending trials early. If new results from equivalent external studies become available, there might no longer be clinical equipoise for the intervention under study, raising ethical issues in continuing the trial. This circumstance can impose a serious ethical issue for participants randomised to the control group, placebo, or outdated standard of care who are undergoing clinical follow-up, as well as for future participants who might be randomised to this less effective (or even dangerous) control group.59,60 Additionally, with other external developments (eg, alternative disease control measures), the intervention being evaluated might no longer be important.

Master protocol framework for global health
The current approach
In global health research, two-arm clinical trials that compare one experimental intervention with the standard of care or placebo (as the control group) are the most often used study design (panel 1). Because there are usually multiple intervention candidates in a given research area, this can result in multiple trials being undertaken independently, with redundant infrastructures created between different trials. These trials also often have different, non-standardised operational procedures; therefore, determining what the optimal intervention for a given condition is becomes difficult when the evidence comes from multiple heterogeneous two-arm trials.61 Some of the current challenges in global health research that arise from the preponderance of multiarm trials, particularly well designed platform trials.62

Different types of master protocols
Master protocols are often categorised as platform trials, basket trials, and umbrella trials (figure 1). Because misunderstanding of master protocols is common, the detailed descriptions of the key concept of platform trials,63 as well as basket and umbrella trials,64 have been
described previously. In brief, a platform trial is a type of clinical trial in which multiple interventions can be evaluated simultaneously by use of a common control group within a single master protocol that shares the same infrastructure with standardised trial procedures. In addition to multiple interventions undergoing multiple interim evaluations simultaneously, platform trials have the additional flexibilities of allowing new experimental arms to be added and for the control arm to be updated if the standard of care changes throughout the trial. Platform trials can minimise the number of participants allocated to the control group by having a common control group. These trials allow for multiple interventions to be evaluated in a perpetual manner while collecting high-quality data that will enable comparisons of the interventions that might be highly relevant in informing new policy changes in global health. For instance, the randomised evaluation of COVID-19 therapy (RECOVERY) trial (ISRCTN50189673 and NCT04381936) is a large, ongoing, adaptive platform trial based in the UK, and this trial has produced important clinical trial evidence that has led to improved inpatient management of patients with COVID-19 worldwide (discussed further in the fourth paper of this Series).

Compared with platform trials, basket trials and umbrella trials are designed to identify therapies that can specifically affect disease targets (targeted therapies), to improve the treatment of diseases. Basket trials evaluate a targeted therapy for multiple diseases that share common disease targets, whereas umbrella trials are designed to evaluate multiple targeted therapies for a single disease that is stratified into multiple subgroups. Because these disease targets are usually determined by their genetic make-up, basket and umbrella designs have predominantly been used in oncology research as biomarker-guided trials. An example of a therapeutic umbrella trial undertaken in LMICs for HIV is discussed in panel 2.

Platform, basket, and umbrella trials are often organised and planned with a modular protocol structure, with the master protocol containing all generic elements of the trial and intervention appendices that are specific to each active intervention. With the use of a modular format, adding a new intervention or discontinuing a current intervention can become more operationally seamless because the main study master protocol does not need to be updated every time a new intervention is added or discontinued in platform trials. In basket and umbrella trials, common screening mechanisms with standardised laboratory procedures are used in different institutions and across different geographical settings under one single master protocol. This standardisation in operating procedures can help to provide harmonisation of clinical trial research efforts across different geographical settings in the global health field.

Benefits of a master protocol framework for global health

Trials planned under the master protocol framework are usually planned for the long term by forming a large trial network across and throughout multiple institutions. Given that common standardised operating procedures are established in multiple institutions through the master protocol, the master protocol framework can allow for a large amount of high-quality data to be collected. The research institutions can also more easily overcome the issues of external changes that might occur during the trial. Should a new therapeutic discovery be made after a clinical trial begins, instead of launching a new clinical trial, the new intervention can be added into the trial and, if there are new changes in clinical practices, these changes could be better adopted into the master protocol and its standardised operating procedures.

Insufficient or poorly organised infrastructure and low human resource capacity for research are often cited reasons as to why high-quality clinical trials are more difficult to carry out in LMICs than HICs. However, clinical trials in global health research are almost always undertaken without any long-term consideration of infrastructure and human resources in LMICs and the likely substantial involvement of external actors in these
settings. Many regions in LMICs have not been given a long-term opportunity to build and maintain ongoing infrastructure that would also allow for local capacity building to be leveraged at the same time. Instead, historically when a clinical trial finishes, the infrastructure usually disappears along with the research opportunities for the local researchers. For many, this outcome results in temporary unemployment and, sometimes, reticence to participate in future clinical trials. For clinical trialists initiating a new trial, recruiting experienced staff is challenging and could delay the trial start date.

Given that master protocols are perpetual in nature, the master protocol framework can help with the capacity building and retention of trained staff under a large, planned collaboration that recruits staff into secure roles for a fixed but long period, in which multiple questions can be addressed over time in one single trial. If the long-term goal is to build the capacity for clinical research in LMICs, then planning for long-term employment is necessary to offer professional development opportunities. Undertaking one large trial under the master protocol framework can also save on resources that are required in setting up multiple independent clinical trials, and savings should be diverted to the health-care professionals based in the sites of investigation, and this framework can identify and address gaps in the research infrastructure that are common barriers to undertaking clinical trials in LMICs.

This cost-saving, which is both a feature of direct and indirect benefits, can instead be diverted to building human resource capacity and research infrastructure in LMICs. In addition to staff training and capacity building, acquisition costs for specialised equipment can be consolidated. For example, the WHO Stepwise Laboratory Quality Improvement Process Towards Accreditation in the African region (also known as SLIPTA) initiative has specifically mentioned the need for experts and centres of excellence in LMICs to improve disease prevention and control. The systemic longevity and specialised methodologies intrinsic to many master protocols should be well aligned with pre-existing efforts, such as the African Strategies for Advancing Pathology, to build on the unique opportunities that the master protocol framework can provide.
Perpetual clinical trials allow for the long-term involvement of the community in the planning of future clinical trials. For these perpetual clinical trials to be meaningful, the scope of research should be driven by local researchers, to correctly target areas that are key priorities in the location of the trial. Key community members (eg, trusted community health-care workers) represent important knowledge translation agents of the trial conduct and study findings for the affected populations. Long-term trust can encourage participant enrolment, retention, and involvement of the dissemination of study findings. Mechanisms to engage with local institutions and ethics review boards can be implemented to enable dialogue around changes in the conduct and evaluation of the trials, to ensure ethical conduct.

**General framework for more efficient trials in global health**

There are several important questions for clinical trial research that deserve consideration during the planning stage (panel 3). These questions can serve as a general framework to improve the efficiency of trials, in global health research and beyond.

In the planning stage, it is important to identify areas of uncertainty and anticipate different scenarios with possible trajectories that might be observed during the trial. There should be extensive discussions with clinical experts based in the area that the trial will be set, and with key opinion leaders with geographical and sociocultural familiarity with that area.

There should be early discussions to identify administrative structures and logistics of data collection, monitoring, and implementing adaptations that could potentially limit the feasibility of undertaking an adaptive clinical trial.

Administrative and operational logistic factors (eg, expected recruitment time and time to implement adaptations) should be discussed with local stakeholders and clinical staff who will be responsible for managing the day-to-day operations of the clinical trial. If the outcome for the prespecified adaption takes a long time to measure in comparison with the recruitment time, adaptive trial designs might not be feasible because the planned recruitment might be completed before a sufficient number of clinical outcomes can be observed.

Whether they are adaptive or not, clinical trial simulations can be used for any trial design and any areas within the global health field. These tools allow trial investigators to explore, compare, and better understand the fragility of assumptions, to produce the most optimal trial design for a given research question.

Simulations allow for an assessment of different designs, including fixed trial designs, for their operating characteristics (eg, expected sample size, type I error rates, and statistical power) under several scenarios. Simulations can also be used to assess other metrics (eg, estimated number of interventions and placebo doses required), to improve resource and operational planning of the trial.

Good simulation practices that have been described for pharmaceutical development can be extended to global health research. Clinical trialists and clinicians involved in the trial do not need to understand every aspect of the statistical assumptions and underlying technical details to partake in group discussions during the planning stage. Because simulations are an iterative process, the initial group discussion on simulation can start with simple simulations to engage the local clinical experts and key opinion leaders and help them to become more familiar with interpreting trial simulation results. Then, in subsequent rounds of simulations, more comprehensive simulations on other more complicated scenarios can be shared for feedback.

Funders could promote the use of simulations and thus more efficient trial planning for global health research if the funders place a requirement for simulations to be included as part of the application process instead of just simple sample size calculations. For instance, when the US Food and Drug Administration recognised the value of simulations and emphasised their use in trial planning, this recognition catalysed the use of simulations in the pharmaceutical industry. Across different LMICs, promotion of simulations will most likely require collaboration and communications between different donors, regulatory authorities, and global health organisations.

**Panel 3: General considerations for efficient clinical trial research**

1. Does the trial ask a question on which there is genuine uncertainty and is the trial design appropriate for answering the question?
2. Does the trial use a control intervention that reflects routine care?
3. Is the trial evaluating interventions that are feasible for use in the setting?
4. Does the trial enrol the population that is most likely to benefit from the results of the trial (show treatment effect)?
5. Have the investigators examined all important uncertainties in the planning stage (eg, examined different control event rates to see how they affect the statistical power)?
6. Have the investigators planned for areas of anticipated regret and other unanticipated changes (eg, planned and implemented a sample size re-assessment during the trial to avoid anticipated regret)?
7. Have the investigators planned for continuity of the treatment or approach to the trial?

**Challenges with adaptive trial designs and master protocols**

**Methodological and operational complexity**

Adaptive trial designs and master protocols can be inherently more methodologically and operationally complex.
complex than conventional fixed trial designs. Incorrectly planned or executed adaptive trial designs can introduce statistical and operational biases. Although more time and resources will be dedicated to the planning stage, this is a far preferable alternative than the current norm of insufficient trial planning practices that occur too frequently in all areas of clinical trial research, including in the global health field. Consolidating resources and collaborations across a wider network of researchers and institutions from different geographical regions will be important for global health research. Instead of creating different control groups, having a common control group can be more statistically efficient. Geographical variability could also be better represented by master protocols because standardised operating procedures will be implemented across different institutions, to record the data into a common centralised database.

Undoubtedly, implementing master protocols will have considerable logistic and operational challenges. For instance, there will be different standards of care across different countries and geographical settings. However, this challenge is not new: many multicentre, multinational clinical trials have successfully overcome similar problems. The rationale for adding a new intervention and the mechanisms should be discussed early with the ethics and regulatory bodies, to ensure that new interventions can be added in a timely manner.

We hope that these challenges will not be used as an argument to deter from the use of these innovative trial design approaches in global health research. Many of these operational challenges and barriers can be minimised in the planning stage by researchers based in the trial setting. Multidisciplinary collaborative efforts can easily overcome the planning challenges.

**Funding challenges**

In global health research, clinical trial funding predominantly relies on grants from government funding agencies and non-profit organisations, and the demand for funding by far exceeds supply. The funding value from the US National Institutes of Health, for example, is usually fixed for all applications that might vary in scope. In practice, clinical trial sample size and trial duration are limited due to budget constraints. Optimistic assumptions about the treatment effects and baseline event rates are picked to justify the sample size that is suitable for the budget, to stay competitive during the application stage. For illustrative purposes, sample size and cost-savings are shown in figure 2. Master protocols and adaptive clinical trials might require more resources than the budget that is typically allowed by the funder.

Under the current funding scheme, the feasibility of undertaking these larger trials is limited even though such trials can improve efficiency and introduce other long-term benefits to staff who are based at the trial location and to local infrastructure. In clinical trials that are sponsored by the pharmaceutical industry, if the trial stops early for either futility or superiority, the remaining budget goes back into the research and development budget to finance other clinical trials. In publicly funded trials that are sponsored by the pharmaceutical industry, if the trial stops early for either futility or superiority, the remaining budget goes back into the research and development budget to finance other clinical trials. In publicly funded trials that are sponsored by the pharmaceutical industry, if the trial stops early for either futility or superiority, the remaining budget goes back into the research and development budget to finance other clinical trials.

![Figure 2: Comparison of two-arm, multiarm, and platform trial approaches on sample size and cost](image-url)

For all scenarios, we assumed that there would be four experimental interventions that will be evaluated. We considered fixed trial designs, in which all clinical trials would end their recruitment in each arm when the target sample size of 650 patients was met. We assumed that a dichotomous outcome will be used as the primary outcome, with pairwise comparison with the control being planned as the primary analysis. The sample size per arm required to achieve 80% statistical power and 5% type I error rate was calculated by assuming an event rate of 40%, an effect size of 20% relative risk reduction, and 10% loss to follow-up rate. Because there are four independent trials being conducted in scenario 1, we defined the maximum total cost (direct and indirect cost) to be US$6·0 million assuming that each of the research grants will be for the amount of US$1·5 million. Detailed explanations are provided in the appendix (pp 2–5). RCT=randomised clinical trial.
with the changing disease burden in LMICs. This approach will require a conceptual change to mandate the funding to be allocated in ways that would catalyse infrastructure and professional development in LMICs.

Conclusion
Adaptive trial designs and master protocols have predominantly been used for research in HICs so far. Increasing awareness and understanding of these concepts will be crucial for global health researchers and their funders, to improve the efficiency and ethics of global health trials. Master protocol frameworks can help to improve the quality of clinical trial research by harmonising research efforts across different LMICs, and they could potentially be used to improve local infrastructure and offer more quality professional development opportunities at the trial setting.

Contributors
JJHP and EJM conceptualised the paper. JJHP, NF, ZAB, KT, MES, and EJM acquired and analysed the data. All authors interpreted the data. JJHP and EJM conceptualised the paper. JJHP, NF, ZAB, KT, MES, and EJM provided administrative, technical, and material support and supervised the study.

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