RESEARCH ARTICLE

REVISED Towards achieving transnational research partnership equity: lessons from implementing adaptive platform trials in low- and middle-income countries [version 2; peer review: 1 approved, 2 approved with reservations]

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Abstract

Background

Use of adaptive clinical trials, particularly adaptive platform trials, has grown exponentially in response to the coronavirus disease (COVID-19) pandemic. Implementation of these trials in low- and middle-income countries (LMICs) has been fostered through the formation or modification of transnational research partnerships, typically between research groups from LMICs and high-income countries (HICs). While these partnerships are important to promote collaboration and overcome the structural and economic disadvantages faced by LMIC health researchers, it is critical to focus attention on the multiple dimensions of partnership equity.

Methods

Based on informal literature reviews and a meeting with leaders of one of the multinational COVID-19 adaptive platform trials, we describe some important considerations about research partnership

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Any reports and responses or comments on the

equity in this context.

Results

We organize these considerations into eight thematic categories: 1) epistemic structures, 2) funding, 3) ethics oversight, 4) regulatory oversight, 5) leadership, 6) post-trial access to interventions, data, and specimens, 7) knowledge translation and dissemination, and 8) research capacity strengthening and maintenance. Within each category we review normative claims that support its relevance to research partnership equity followed by discussion of how adaptive platform trials highlight new dimensions, considerations, or challenges.

Conclusion

In aggregate, these observations provide insight into procedural and substantive equity-building measures within transnational global health research partnerships more broadly.

Keywords
international research partnership; equity; adaptive platform trials; adaptive clinical trials; public health emergencies

article can be found at the end of the article.

This article is included in the Global Infectious Disease Ethics Collaborative (GLIDE) gateway.

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REVISED **Amendments from Version 1**

Revisions to this manuscript have been made based on the suggestions of the three reviewers in addition to some text and phrasing revisions to allow for clarity. Major revisions include elaborating on the methodology used to generate review results, restructuring of the results section and expansion of Table 2, addition of a brief discussion section, and the addition of boxed text to highlight in-depth examples.

Any further responses from the reviewers can be found at the end of the article

Introduction

Recent infectious disease epidemics and pandemics have brought increased attention to the use of clinical trials that deploy adaptive designs. This term encompasses a wide range of trial designs that allow for predetermined opportunities to modify a protocol based on interim data analyses, and enact statistical and operational adjustments while maintaining the validity and integrity of the final trial results[1,2]. Adaptive platform trials compare multiple interventions against one another, commonly sharing a singular control group and adding or dropping intervention arms based on predefined decision points and cumulative data evaluation. These types of trial design were already familiar to some endemic infectious disease research (e.g., the PanACEA tuberculosis trials) and non-communicable diseases research, particularly in oncology. However, increased attention to adaptive platform trials arose in response to recent global infectious epidemics and pandemics. In particular, the results of several large multinational adaptive platform trials (e.g., RECOVERY[3–5], SOLIDARITY[6], and Randomised, Embedded, Multi-factorial, Adaptive Platform Trial for Community-Acquired Pneumonia (REMAP-CAP)[7]) were critical to global discussions and guidance formation for managing coronavirus disease (COVID-19)[8]. During an epidemic or pandemic where countless lives are at risk, there have been arguments that favor this type of trial design on both operational grounds (large-scale clinical trials with conclusive results emerging more quickly to dictate clinical practice) and ethical grounds (minimizing the number of participants randomized to control arms and boosting the anticipated benefit to risk ratio given ability to add or drop interventions based on efficacy and safety). Adaptive platform trials are also viewed by some as being more 'synergistic' with clinical management by providing a panel of potential therapeutic options as is done in clinical medicine, minimizing the chances of a participant receiving no intervention, and being more adept at responding to constantly evolving medical knowledge, clinical care, and public policy shifts during outbreak response[9].

In response to the COVID-19 pandemic, adaptive platform trials were rapidly implemented in the United States and Western Europe[10,11]. As the pandemic progressed, the need for low- and middle-income country (LMIC)[1] inclusion became evident. As a result, several adaptive platform trials fostered research partnerships and incorporated LMIC study sites as they had for other outbreaks (Table 1), such as the Ebola virus. Transnational partnership between two or more international collaborators is a common model for externally funded health research in LMICs. While partnerships between two or more LMICs are important[12], many if not most international clinical trial partnerships are between high-income countries (HICs) and LMICs[13,14]. HIC partners[2] often contribute financial resources and scientific experience, to complement LMIC partners' resources, scientific capabilities and experiences, social capital, and understanding of the local health and health research landscape. These types of partnerships are prioritized as one of the United Nations' Sustainable Development Goals (SDGs)[15] and equity between partners is considered essential for ethical partnership-based research in LMICs[16]. We define "research partnership equity" as collaborative and inclusive research practices that incorporate fairness of opportunity and prioritize mutually beneficial inputs, processes, outputs, and impact. Equity is a foundational principle of the conduct and outcomes of global health research[17] with its justification grounded in theories of global justice[18,19].

However, these partnerships are not without challenges. In many LMICs, it can be particularly difficult to acquire and produce scientific knowledge due to historical, structural, economic and geopolitical influences that impose disproportionate capability limitations. Imbalances and differences in terms of partner experience, research interests, institutional support, and access to financial and material resources[20] – among other considerations – risks inequitable and suboptimal outcomes. This is compounded by the fact that some of these imbalances can be rooted in the historical colonialization of many LMICs,

[1] The term 'LMIC' is used throughout this report in reference to countries that fall under World Bank criteria for low- and -middle income countries as defined by gross national income per capita. This terminology is used widely in academic literature but is an imperfect descriptor that fails to capture important distinctions and variability between countries that make them independent world entities. By using this term, we do not wish to suggest there is uniformity of experiences of these countries with international research partnerships or during public health emergencies because of their income status.

[2] We use the non-specific term 'partners' to be inclusive of wide variety of stakeholders who centrally contribute to transnational research partnerships. In our discussion of partnership equity, we interpret 'partners' to mean HIC or LMIC stakeholders with, or with the potential to achieve, equivalent positioning and overlapping responsibilities; for example: investigators, research staff, and/or institutions. Providing funding for research activities does not, on its own, make a sponsor a partner under this definition; yet transnational research sponsors have certain obligations to foster and financially support structures and activities that advance partnership equity, in our view. While beyond the scope of this paper, an in-depth analysis of specific roles and responsibilities of research sponsors towards partnership equity would be of value.

Table 1. Examples of platform adaptive clinical trials involving low- and middle-income countries (LMICs).

Type of adaptive design	Description	Examples	LMIC involvement
Multiarm multistage (MAMS)	Compares multiple experimental groups against a shared control group. Permits early stopping of non-promising or highly effective arms and/or initiation of new arms using prespecified criteria.	RECOVERY (coronavirus disease [COVID-19])	Ghana, India, Indonesia, Nepal, Vietnam
		SOLIDARITY (COVID-19)	Bangladesh, Bolivia, Egypt, Ethiopia, Honduras, India, Indonesia, Iran, Kenya, Lebanon, Mali, Mozambique, Niger, Nigeria, Pakistan, Philippines, Sierra Leone, Zimbabwe
		CROWN-CORONATION (COVID-19)	Ghana, Zambia
		TB-PRACTECAL (Tuberculosis)	Uzbekistan
		TRUNCATE-TB (Tuberculosis)	Indonesia, Philippines
		PALM (Ebola)	Democratic Republic of the Congo
Response-adaptive randomization (RAR)	Allows for changes to the randomization probabilities based on interim analysis of ongoing trial results.	PREVAIL II (Ebola)	Liberia, Sierra Leone, Guinea
		REMAP-CAP (COVID-19)	Pakistan, India, Nepal

with contemporary structures echoing systematic oppression and maintaining barriers to intellectual and scientific leadership among LMIC investigators and research groups[21]. These asymmetries can be directly or indirectly reflected in organizational contracts and memoranda of understanding used in research partnerships, influence allocation of research funding, impact the availability of local scientific mentorship and methodological training for core capacity strengthening efforts, and perpetuate asymmetry in research partnership outputs.

There is widespread acknowledgement of research partnership inequities[22–24] as well as a growing literature of qualitative studies contextualizing recurrent themes within research partnership equity[25–27]. Scoping reviews of guidance frameworks suggest emerging consensus around the major themes that contribute to research partnership equity[28,29]. There are also dedicated efforts – such as the Research Fairness Initiative led by the Council on Health Research and Development[30] and the Equity Tool for valuing Global Health Partnerships developed by the Canadian Association for Global Health[31] – to evaluate equitability of collaborating partners. Yet the operationalization of equity recommendations in research partnerships remains poorly understood and has largely been restricted to descriptions of program practices[32], anecdotal commentaries and opinions, condemning 'parachute' or 'parasitic' research practices[22,33], or limited to discussions about authorship[34–36] and bibliographic trends[37]. While these efforts are necessary and important, they are not sufficient to claim that the complexities around research partnership inequities are fully understood nor have optimal mechanisms for preventing them been identified.

In this report, we describe what can be learned about research partnership equity from the experiences of implementing multinational adaptive clinical trials during the COVID-19 and Ebola pandemics with a particular emphasis on adaptive platform trials. We offer a thematic analysis of eight categories where asymmetries exist within transnational research partnerships: epistemic structures, funding, ethics oversight, regulatory oversight, leadership, post-trial access to interventions, data, and specimens, knowledge translation and dissemination, and research capacity strengthening and maintenance (Table 2). For each category, we first discuss general considerations including the normative claims that have been offered previously in efforts to promote equity in transnational research partnerships. Key examples are highlighted in boxed text. This is followed by some of the unique ways in which adaptive platform trials contribute their own complexities and potential solutions to research partnership equity issues. While these issues are important for all types of global health collaborations, they are heightened in the adaptive platform trial context because of the coordinated multinational reach, dynamic adaptability of research objectives, and substantial investment in scientific infrastructure that are associated with them. We emphasize how implementing these trials can highlight opportunities to narrow equity-related asymmetries between LMIC and HIC research partners.

Methods

This analysis was produced as a part of commissioned project focusing on ethics and adaptive clinical trial designs in public health emergencies conducted with support from the World Health Organization (WHO) Ethics and Governance

Table 2. Summary of general challenges and proposed solutions within international research partnership equity plus pertinent take-away points relevant for multinational adaptive platform trials.

Theme	Challenges	Proposed solutions	Considerations for adaptive platform trials
Epistemic structures	• Scientific literature and globally-acknowledged expertise remain concentrated in high-income country (HIC) settings. • Low- and middle-income country (LMIC) partners are often regulated to the role of 'data collectors' and are provided with fewer opportunities to be involved in study design and data analysis.	• Clear expectations about the generation of data and knowledge should be outlined explicitly in contracts or memorandums of understanding and reinforced by the institutional and financial sponsors supporting the research. • Requires investment in the professional development of LMIC researchers to contribute to research design and implementation[38–41]. • External resources can be leveraged, for example the World Health Organization's (WHO's) HINARI and Research4Life platforms that provide journal and literature access to low-income country institutions at low or no cost.	• HIC partners likely have disproportionate adaptive trial methodological expertise within a transnational partnership. This is one of the inherent imbalances that needs to be accounted for when determining goals for the partnership, concordance with local research objectives, LMIC research capacity, and plans for research dissemination and innovation.
Funding	• Research agendas and priorities are often dictated by funders based in HICs that are less relevant or have limited adaptability to LMIC-specific needs. • Funding is often available for a limited duration or specific project with less attention toward sustainability and investment in LMIC research infrastructure.	• Work with funders at an institutional and policy-level to include diverse LMIC perspectives during the earliest stages of establishing research networks and priorities. • Justifications for priorities decided upon need to be clearly outlined by a funder and endorsed by LMIC leadership and health officials. • A careful balance is required with expectations about duration and contributions of international funding for LMIC health priorities and how they factor into long-term sustainability and promotion of local funding mechanisms.	• Prior to the coronavirus disease (COVID-19) pandemic, global health funding mechanisms were less familiar with adaptive platform trials and the budgets were not always sufficient. This limited the feasibility of conducting adaptive trials overall, but particularly within LMICs. • Significant up-front investment in adaptive trials can provide a degree of financial security provided there is dedicated time and effort to incorporate domestic and other sustainable mechanisms of funding long-term.
Ethics oversight	• Despite major improvements in research ethics committee (REC) capacity, infrastructure and resources for ethical oversight remain underdeveloped in many LMIC contexts.	• Partnering with or providing support to LMIC RECs would help with the increased burdens associated with oversight of large research partnerships, especially during public health emergencies[42,43]. This could include fostering partnerships between committees to help provide mutual support and perhaps even collaborative review of research proposals[44–47]. • Ethical oversight during public health emergencies that goes beyond IRBs is also developing, including efforts such as the PREPARED initiative.	• There is a need for REC familiarity with adaptive platform trial designs including unique ethical considerations of these methodologies, as this may not fall under the expertise of many LMIC and HIC RECs. • Partnering with or providing support to LMIC RECs would help with building this expertise.
Regulatory oversight	• Regulatory oversight requires a careful balance of mechanisms that protect LMIC research participants and communities from exploitation without imposing insurmountable restrictions on research partnerships and institutions.	• National regulators should bear at least some of the responsibility for monitoring the implications of blunt research oversight policy actions[48,49]. • This includes re-evaluating processes for recognizing the legitimacy of alternative regulatory frameworks[40,50].	• Many sponsors have limited experience co-supporting research with other sponsors which is a common model for funding large multinational platform adaptive trials. • LMIC-specific guidance for the regulatory oversight of multinational adaptive trials is needed as current guidance is developed mostly for HIC-only contexts.

Wellcome Open Research 2023, 8:120 Last updated: 11 DEC 2023

Theme	Challenges	Proposed solutions	Considerations for adaptive platform trials
Leadership	• Leadership often defaults to the HIC partner who has increased access to professional and research-related resources, including funding and institutional capacity.	• Leadership can take many different forms, and within a research partnership there needs to be acknowledgement of the different strengths leaders from LMICs can contribute when compared to those from HICs.	• Concentration of HIC leadership within adaptive trials can be avoided by early inclusion of LMIC partners in the study simulations and design and rotating distributive leadership positions.
Post-trial access to interventions	• Guidelines for post-trial access vary in their recommendations. • Providing post-trial access may be more realistic for some types of research and partnerships over others, and some LMIC research partners may prioritize other types of study benefits, such as investment in scientific capacity and infrastructure.	• At minimum, post-trial access to interventions must be negotiated early during the research process and be mutually agreed upon by both LMIC partners, HIC partners, and LMIC health policymakers[41,51]. • Transparency with research participants should be incorporated into the study protocol and informed consent processes[52,53].	• Post-trial access to interventions within adaptive platform trials is complicated by the dynamic nature of the research design. • Flexibility in adaptive platform trials may make them a more appropriate research design in some settings when there are feasibility concerns regarding post-trial intervention availability (i.e., study arms would only utilize feasible interventions).
Post-trial access to data and biospecimens	• Careful attention is needed to who 'owns' and 'allows others' to access study data and specimen repositories and whether groups that govern this information, which are most frequently based in HICs, gain a disproportionate amount of power in the form of knowledge production and distribution.	• Research resource sharing should be bidirectional and ought not preclude LMIC access to data and specimens. • Investment in equalizing these resources between research partners – including information technology and biobanking support – is needed as a part of the partnership plan and funding. • Guidance on scientific data management and stewardship is available, for example the FAIR Guiding Principles[54,55], although these recommendations do not comment specifically on who has, or should have, data access.	• Large amounts of data collected within multinational adaptive trials can help highlight LMIC-specific trends or findings that impact local practice or provide point-of-comparison outcomes relative to other geographic areas involved in the study.
Knowledge translation and dissemination	• Research efforts with limited utility to LMIC settings rarely translate into meaningful outcomes for the community.	• Consideration needs to start as the research agenda is being set, given that research that is responsive to local priorities is most valuable to policy and practice. Involvement of key policy and practice stakeholders from study initiation through publication and dissemination can improve the likelihood of uptake, especially if those individuals are also in positions to directly apply the results of the research[56,57].	• Adaptive platform trials necessitate clear explanations for how the research design may have impacted interpretation of the results should be available for implementers and policymakers.
Research capacity strengthening and maintenance	• Traditional global health funding mechanisms and research partnerships often de-prioritize or inadequately address LMIC administrative, institutional, and research capacity strengthening. • Short-term sponsor-initiated timelines often preclude the time needed for meaningful capacity building.	• Begin with a series of consultations to identify needs and continue through all research-related and post-trial partnership activities. • Dedicated measures towards research capacity strengthening, including research and ethics training, mentorship, statistics and epidemiology guidance, and academic writing workshops, should be implemented in parallel with traditional research procedures.	• The sizable financial and research training investment required to establish a large, adaptive platform trial may be uniquely positioned to provide built-in protections for research capacity strengthening efforts, provided there is ongoing attention to sustainability.

Wellcome Open Research 2023, 8:120 Last updated: 11 DEC 2023

Unit. The intended audiences of this project are researchers, institutions, funders, and sponsors who currently or plan to engage in multinational adaptive platform clinical trials. We performed a rapid narrative review[58] on transnational research partnership equity, which was cross referenced with selective reviews of literature on adaptive clinical trial designs and adaptive platform designs, including those reporting COVID-19 and Ebola research in order to answer the following question: what transnational research partnership equity considerations are relevant to adaptive platform clinical trials? This approach allowed for broad examination of emerging evidence, evaluation for more specific lines of inquiry, clarification of concepts, and synthesis of two largely separate but theoretically converging lines of published literature.

The PubMed/MEDLINE, Scopus, and Google Scholar databases were reviewed in March and revisited in May of 2022 by authors CM and PS using keyword searches for 'equity' OR 'fairness' AND 'international research partnerships' OR 'global research partnerships' 'OR 'transnational research partnerships' OR 'North-South partnerships.' Eligibility criteria included postings which: 1.) described or categorized the components of international research partnership equity; 2.) were peer-reviewed and featured primary empirical research, published guidelines or policies, program reports, normative/conceptual articles, or commentaries/editorials; and 3.) were published in English. There were no publication date specifications. The selective literature search on adaptive clinical trials focused on ethical analyses and operationalization of these trial designs and included search terms 'adaptive clinical trial +/- designs' OR 'platform trial' AND 'ethics' OR 'ethical considerations' OR 'experience' OR 'operationalization.' OR 'implementation.' Eligibility criteria were the same as listed above. The citations were appraised and relevant postings were included in subsequent abstract and full-text reviews. Searches were conducted by two independent reviewers who met to discuss findings and develop and apply thematic categorizations. Any variation in interpretation or classification of findings was resolved by consensus. Because of the limited project timeframe, further systematic tracking of the literature was not pursued. One of the limitations of this approach is that we cannot exclude any potential bias introduced from an informal review as opposed to using a more formal approach, perhaps limiting the replicability of our findings. Additionally, the definition and components of research partnership equity are evolving over time complicating literature identification.

To enhance understanding of the literature and identify some unpublished experiences and practices, an informal virtual meeting with the leadership teams of the Randomised, Embedded, Multi-factorial, Adaptive Platform Trial for Community-Acquired Pneumonia (REMAP-CAP) was held via Zoom in April 2022. Notes taken from this meeting were integrated into the working themes identified from the literature reviews (including areas of congruence and conflict), discussed between the authors until consensus was reached, and a preliminary report was drafted. This report was then discussed during a project group meeting in Geneva, Switzerland in July 2022. Findings were iteratively revised based on feedback from this meeting, including areas relevant to the scope of this report compared to other aims of the project, and from critical review by experts in ethics, global health, and adaptive clinical trial methods who provided staged feedback on preliminary drafts of this report.

Results

Epistemic structures

Challenges. Production of valid scientific results requires not only the resources to generate new knowledge, but also the means to access epistemic structures (i.e., how knowledge is defined, acquired, and categorized) including systems of scientific publication and dissemination of research. Despite recent growth in open-access publication[59], much of the relevant global health data and scientific literature remains concentrated in HIC settings with LMIC researchers often dependent on global health organizations, HIC sponsors, or HIC research collaborators to access these knowledge bases. There is a risk of defaulting to HIC-centric conceptions of what constitutes meaningful data and health outcomes without necessarily recognizing the extent to which culture, language, and context can influence meaning[60].

In terms of knowledge production within a research partnership, LMIC researchers are sometimes limited to the role of 'data collectors,' responsible for assembling samples and engaging in research fieldwork[25,61]. HIC researchers often have a stronger voice in determining who conducts and verifies analyses, and what is included in final products for dissemination. This is reflected in an evaluation of international randomized clinical trials which found that across 305 clinical trials, data flowed exclusively from collection in LMICs to analysis in HICs for 73% of studies[62]. This dichotomization between partner responsibilities not only underutilizes existing skill sets, but also limits LMIC researchers' participation in activities that contribute to study design and interpretation of data[63] when integrating LMIC perspectives can actually provide more validity to the work.

Considerations for adaptive platform trials. With respect to adaptive platform trials, a systematic review of master protocols found growing uptake of these designs worldwide; however, their use has been almost exclusively restricted to HICs[64]. It follows that the majority of experience in the methodological design and conduct of adaptive platform trials to-date likely resides within HIC investigators and institutions. If this holds and HIC partners have disproportionate methodological expertise within a transnational adaptive trial partnership, this provides an opportunity for partnerships to orient some of their goals towards increasing methodological capacity of LMIC researchers.

LMICs were initially not included in the majority of multinational clinical trials established early during the COVID-19 pandemic. Adaptive platform trials investigating a wide range of therapeutics rapidly started across thousands of sites in the United Kingdom, European Union and United States where the study designs and protocols for these trials were developed and implemented. Eventual inclusion of international sites, including in LMICs, required a careful balance. On one hand there are the universal objectives of a

centralized research regarding the need for data generated at newly added sites to be compatible and comparable to the rest of the study (i.e., a universal protocol). On the other hand, attention to the interests of LMIC researchers and communities need to be respected and incorporated into the trial design and its implementation. That is, there is a need for taking a pluralistic approach to the needs of different populations. This includes pragmatic assessment of what therapies and interventions will realistically become available within a particular LMIC, which vary when compared to interventions in HICs. Additionally, while research data may need to be aggregated for some of the primary analyses in a multinational trial, local data should ideally be available for independent analysis by LMIC (as would be true for any country) researchers for specific trends or findings that may impact local practice. One of the benefits of adaptive platform trial designs is that addition or removal of study arms according to feasibility or needs of specific LMIC settings is possible. The debates about universal versus plural approaches to global health research are not new[65]. Growing experience with multinational adaptive designs is an opportunity to provide further empirical evidence about how these approaches influence the design and implementation of research.

Box 1. The Randomised, Embedded, Multi-factorial, Adaptive Platform Trial for Community-Acquired Pneumonia (REMAP-CAP)

REMAP-CAP provides a helpful example of operationalizing adaptive platform trials in LMIC settings[7,57,66,67]. The roll out of REMAP-CAP in several LMICs in Asia was facilitated by partnering with an existing research network, the Collaboration for Research, Implementation and Training in Asia (CCA), which had overlapping research interests and allowed them to operationalize trial arms in India, Nepal, and Pakistan[57]. Development of mutual goals and outcomes was enabled by establishing a LMIC-led local governance body to interface between REMAP-CAP leadership and local LMIC study sites. This helped to support early identification of feasible interventions and incorporation of LMIC investigators into the international steering committee, both of which allowed for integration of LMIC perspectives and input at multiple levels of the multinational platform trial.

Funding mechanisms

Challenges. Much of the power asymmetry between HIC and LMIC partners is believed to be rooted in access to funding[68,69] which can perpetuate inequities in the ability to apply for funding when available. The research agenda and priorities of a transnational partnership are frequently indirectly driven by HIC partner interests or dictated by funders based in HICs seeking global collective insight and scientific advancement. Typical processes for setting research agendas can overlook or underestimate pressing but less universal LMIC-specific needs[43,70] and inadequately address the complex societal influences that disproportionately contribute to poor health outcomes in LMICs such as poverty, food insecurity, poor sanitation, and limited healthcare infrastructure. Major donors in both the public and private sectors are more likely to fund HIC researchers and, while increasingly interested in health equity, have been relatively absent from conversations about promoting research partnership equity[46]. This results in LMIC researchers reporting the need to compromise on interest or relevance in order to access personal and research-related financial support[25]. HIC partners tend to be approached first to weigh in on how to structure a partnership, including assigning group-level responsibilities, establishing an activity timeline, and allotting research resources. As described by Kalinga[47] "Those who hold the purses dictate the terms." Because of the close relationship between prominent funding models and setting the research agenda, advocating for the interests and needs of LMIC communities may seem to be beyond the ability of individual HIC and LMIC partners to address.

Box 2. The Ghanaian-Dutch Health Research for Development Programme (HRDP)

Challenging this asymmetry between the research agenda set by funders and research needs of LMIC communities is the HRDP, which ran from 2001–2008 in response to concern that the research priorities of LMICs were not being supported through traditional funding mechanisms. The Dutch government collaborated with Ghanaian researchers and showed that supporting demand-derived, LMIC-led research resulted in products that were likely to be implemented and used to inform health policy in Ghana. Partnerships with Netherlands-based researchers did occur in some instances as part of this collaboration, but the role of these HIC partners was described more as one of allyship and support to LMIC partners than direct involvement and leadership[56]. The HRDP came to an end in 2008 after sponsorship support for the program from the Dutch government ended.

Considerations for adaptive trials. Funding for adaptive trials is susceptible to the same issues of funding global health research more generally. Prior to the COVID-19 and Ebola outbreaks, traditional global health funding mechanisms were less familiar with adaptive platform trials and the budgets awarded were not always sufficient to meet the needs of very large research networks and associated complex protocol development and study implementation requirements[71]. This limited the feasibility of conducting adaptive trials overall, but especially in LMICs[64]. All of this has changed with COVID-19, but the long-term ramifications of this shift in interest and funding allotment have yet to be fully actualized. Early dedicated funding to the initiation of these large trials led to their rapid scale up in HICs, partially driven by priorities of the funders to form study sites and enroll participants from the funder's own country[9].

Adaptive platform trials are complex trials to design and implement. They also require significant upfront investment from industry and other clinical trial sponsors. Upfront financial commitment can protect against the risks that come with unpredictable funding, such as compromise in research outcomes or falling short of projected research capacity strengthening efforts. Further, early, large financial commitments allow for more time to incorporate domestic and other more sustainable mechanisms for long-term funding. However, all of this seems to require that LMIC partners are included in financial discussions from the beginning of the research process and design.

Ethics oversight

Challenges. While some LMICs have robust mechanisms for local ethics and regulatory oversight of research[72], oversight infrastructure and resources remain underdeveloped in many LMICs, relative to HICs[73]. There have been major efforts and improvements in research ethics committee (REC) capacity[74,75] to address the growing scope of ethical concerns around health research in LMICs as well as increasing attention to the role of community advisory boards (for further discussion on this, please see *Davies et al.*[76] in this series).

Box 3. Joint Scientific Review

The WHO-African Vaccine Regulatory Forum (AVAREF) brought together multidisciplinary teams of experts to review multinational vaccine trials during infectious disease outbreaks that shortened protocol review timelines and supported LMIC REC capacity strengthening[77]. Similarly, the Global Emerging Pathogens Treatment (GET) consortium, which engages multidisciplinary African leaders in surveilling and responding to local and national public health emergencies, published its deliberations and approach to ethical review during the Ebola response, establishing an African-led framework for future epidemics[78].

There is a need for more familiarity with adaptive platform trial designs amongst RECs, including unique ethical considerations of these different methodologies[79]. Another article in this series provides additional analyses of the ethical considerations unique to adaptive platform trials[50]. This may not fall under the current expertise of many committees, particularly in LMICs where adaptive trials are a recent development. This issue is not isolated to LMICs, however. Delays associated with ethical review of adaptive trials have been noted in the European Union as well[66]. Appropriate training and guidance to RECs on evaluating protocols and justifications for adaptive platform trials is an important part of building local research capacity and helps avoid rejection of scientifically valid research based on methodological unfamiliarity[49].

Regulatory oversight

Challenges. Regulatory oversight in transnational research is highly variable and has been criticized in some situations as being too restrictive with the use of a universal or 'one-size-fits-all' approach to research monitoring without appreciating the nuances and complexities that come with different research study sites and resources[80]. For some LMIC research regulators, motivating factors for imposing local restrictions and requirements have included general concerns about 'outsourcing' clinical research that would traditionally be regulatorily challenging to pursue in HICs[81,82]. While research participant protection has arguably been a target of these efforts, some regulatory actions have come at the cost of making research difficult to conduct. For example, in India[83] and Chile[40], the number of operating clinical trials decreased after requirements related to compensation for overly broad definitions of trial-related harm and stringent consent requirements were imposed.

It is noteworthy that when seemingly burdensome regulatory requirements emerge within a small number of jurisdictions, even if they are well-justified, those who have control over global health research resources may simply elect to fund research elsewhere. This can lead to the perception that health research in LMICs operates in a privileged space wherein HICs can find an alternative research site while LMICs are not afforded that flexibility. Such an ability offers a paradigmatic reflection of the inequitable distribution of power between those who fund research and those who may benefit from its outputs.

Considerations for adaptive platform trials. Adding complexity to the oversight context, large multinational platform adaptive trials typically have multiple sponsors form across different countries, who may or may not have a history of co-funding research. Large, multinational platform trials that are well- and variably-resourced to address an epidemic or pandemic can make accountability and responsibility more confusing for both sponsors and regulators who may not have the experience or frameworks to coordinate with other sponsors or fulfil their roles in an organized manner[9]. The International Conference of Harmonisation Good Clinical Practice Guidelines (ICH-GCP)[84], which among other things enumerates sponsor responsibilities, seem to assume a single study sponsor. In addition, although basic regulatory and design requirements for clinical trials using adaptive methods are available from the U.S. Food and Drug Administration (FDA)[85] and the European Medicines Agency (EMA)[86], these are recommendations based on experiences and regulatory bodies situated in HICs. For example, the FDA report Adaptive Designs for Clinical Trials of Drugs and Biologics Guidance for Industry[85] details the complexities of planning for simulations to reduce statistical errors that are specific to potential components of adaptive platform trials such as adaptations to treatment arm interventions or evolving endpoints. It is possible that expertise in these advanced statistical methods is limited in LMICs and other under-resourced areas and there is no formal guidance for how to develop this skill set where it did not previously exist, leaving it up to the discretion of individuals partnerships. While this may not necessarily be within the scope of the FDA to determine, special regulatory considerations for internationally funded adaptive trials conducted in LMICs, and LMIC-specific guidance for these trials, including capacity development recommendations or requirements, is needed. A more detailed discussion of regulatory cosniderations for adaptive platform trials can be found in another article in this series[87].

Leadership

Challenges. Leadership in collaborative trials can default to the HIC partner who typically has greater access to financial, training and material resources. Attempts to incorporate LMIC leadership can be perceived as tokenistic if relevant roles and responsibilities are not clearly discussed and delineated in formal research partnership agreements and actions and with an eye toward equity. Within more localized and LMIC-specific epidemics, there is even more reason to ensure leadership is representative of the local research context.

For longitudinal research programs, the transfer of leadership from HIC- to LMIC-based researchers is often advocated for but can sometimes be hindered by institutional and individual-level factors. But this is not always the case and there are many examples of partnerships that have enacted very intentional efforts in the training of LMIC leaders and transfer of partnership responsibilities.

Box 4. Partnership for Research on Ebola Virus in Liberia (PREVAIL)

In 2014, discussions initiated by the Liberian minister of health[88] were held with the National Institutes of Allergy and Infectious Diseases (NIAID) in the United States, which funded and formed PREVAIL to assess experimental interventions in response to the Liberian Ebola epidemic. This partnership subsequently evaluated two vaccine candidates for prevention (PREVAIL I)[89] and designed an adaptive study protocol to evaluate potential treatments (PREVAIL II)[90] among other Ebola-related studies[53,91]. Within these studies, LMIC leadership was recognized as making highly important contributions to the social mobilization and communication of Ebola prevention, including the formation of community-based task forces and support for individuals isolated under quarantine[88].

Considerations for adaptive platform trials. Leadership and experience with adaptive trials, especially those addressing global pandemics such as COVID-19, has the potential to be concentrated to HICs where the majority of the centralized protocols are initially developed. This could be mitigated by early inclusion of LMIC partners in the study simulations and design. Because of their wide distribution and geographic range, it has been recommended that leadership within multinational adaptive trials not be isolated to one or a few individuals but be viewed more as 'distributive leadership' with a rotating steering committee and a separate intervention prioritization committee so power, influence, and decision-making are not concentrated within a small group of individuals[9].

Post-trial access (PTA) to interventions, data, and specimens

Challenges. Discussions around post-trial access are often delineated between 1.) access of study participants and the community to study-related interventions; and 2.) access of research partners to study data and specimens. Both are relevant to research partnership equity and adaptive trial design. The terms of PTA to study data, lab specimens, and interventions are ideally delineated prior to onset of collaborative trials in LMICs. This is admittedly a complex process and PTA access plans can sometimes be impossible to implement, particularly for study-related interventions[51]. Frequently, there are local expectations of access to these resources; yet, more often than not continual access is challenging for LMIC partners[92,93].

Post-trial access to interventions found to be beneficial is a long-standing issue in global health research and often is viewed as a matter of global distributive justice[18], requiring input from stakeholders beyond a research partnership including local health officials and policymakers. International and national guidelines for post-trial access vary in their recommendations, stances on necessity, and details of how post-trial access should be secured[55].

Research resource sharing should be bidirectional and ought not preclude LMIC access to data and specimens, which has historically been the norm. There are growing calls for universally-available research data repositories and specimen biobanks to promote and replicate medical discoveries on a global scale[94,95]. While this has the potential to contribute to advancement of multiple research agendas, there are significant ethical tensions around informed consent, data security, return of results, and governance of unknown downstream research activities.

If LMIC researchers and policy makers are dependent on the HIC groups to access data sets relevant to their population's health, this can set back goals of developing robust, integrated national health information systems. It also has the potential to propagate use of health metrics and indicators designated as important by HIC-based researchers, epidemiologists, and public health experts, which may not necessarily translate into local ways of interpreting health outcomes[96].

Box 5. The International Network for the Demographic Evaluation of Populations and Their Health (INDEPTH)[97]

INDEPTH serves as an example of a current LMIC-led data repository for longitudinal demographic health data in 52 countries. Access is provided to contributing institutions, and support teams based in South Africa and India are available to assist with technological barriers and formatting study data for the repository to offset this burden from study staff and investigators.

Considerations for adaptive platform trials. In adaptive platform clinical trials, PTA to successful study-related interventions and biospecimens can be complicated by the dynamic nature of the research design as the final intervention or research population is not always the same as when the trial started. Adaptive platform trials during the COVID-19 pandemic included widely available therapeutics (e.g., aspirin) and novel therapeutics (e.g., monoclonal antibodies) at various points of time. Due to a combination of limited global availability and stipulations of the pharmaceutical companies sponsoring these trials, it was often not realistic to expect novel therapeutics to be available post-trial in LMICs[9]. Intervention arms therefore focused on treatment options that would be locally feasible to implement, which were often repurposed medications. In such a context, consideration of PTA is needed not only during the initial planning stages, but also when significant modifications to the interventions or research protocol are made. This ensures ongoing transparency and realistic expectations.

Knowledge translation and dissemination

Challenges. The impact of health research is minimal unless it is translated into clinical practice, health systems, or health policy. Efforts by all partners need to be made to transform research results into products and languages that are relevant to and can be understood by health system leadership and staff, research participants, local communities, and health policy personnel. This includes a need to prevent miscommunication about research results and rectify misinformation if it arises.

Considerations for adaptive platform trials

For trials using adaptive platform designs, clear explanations for how the research design may have impacted interpretation of the results should be available for clinicians and other key stakeholders to accurately interpret findings. Lack of familiarity with the methodology of these trials may result in confusion during their clinical implementation. This is especially pertinent during an epidemic or pandemic where research findings may be implemented rapidly. Trial partnerships should prioritize effective communication about clear conclusions resulting from the data as well as limitations and when there may be variation in interpretation. Issues like these differences need to be incorporated into discussions about policy and practice translation by inviting pluralistic analyses and interpretations of research data and conclusions. It is particularly important to include those with expertise in local contexts, and what these differences would mean in terms of health policy actions taken in response to this new scientific knowledge. Doing so requires a firm foundational knowledge of how trials are designed and associated limitations of specific methodologies.

Box 6. Ebola ça Suffit Ring Vaccination Trial

Ebola ça Suffit was a stepwise cluster-randomized vaccine trial initiated in response to the Ebola outbreak in West Africa between 2014-2016. The methodology of using ring vaccination was actively debated[98] based on its deviation from using placebo-based control groups (similar to more recent discussions around adaptive platform trials). The initial study reported a statistically significant estimate of 100% protection from Ebola among individuals within the clusters[99]. Subsequently, a committee formed by the U.S. National Academies of Sciences, Engineering, and Medicine challenged this result using an intention-to-treat model that demonstrated a much lower vaccine efficacy rate of 65%, which did not reach statistical significance[100]. These are arguably clinically- and policy-relevant discreapncies in how to interpret the same data.

Research capacity strengthening and maintenance

Challenges. Equity within transnational research partnerships requires dedicated attention to capacity strengthening to support sustainability of methodological and other research capabilities. While it is important for all partners to enhance their research skills and experience, the greater academic, institutional, and economic resources at the disposal of HIC researchers argues for focusing research capacity efforts on the LMIC partners. This does not preclude the important of HIC capacity building, particularly in understanding LMIC contexts and needs as well as evaluating internal power dynamics to determine how HIC-based institutions, researchers, and sponsors can initiate or transition into positions of allyship instead of leadership.

Careful attention to each partner's strengths, capabilities and needs is important to the productive identification of capacity strengthening opportunities that are mutually embraced, and potentially even mutually beneficial[101]. Capacity strengthening that is targeted to specific needs is far more impactful than generic approaches, and it can take time to build relationships of trust that support meaningful building of knowledge and skills. Similarly, the capacity to translate research findings into policy and practice is felt to increase as programs and partnerships mature and gain experience over time[102].

Considerations for adaptive platform trials. The lack of established research infrastructure and capacity to support rapid expansion of complex clinical trials was a central barrier to LMIC participation in large adaptive platform trials early in the COVID-19 pandemic[9]. Participation of the few LMIC sites that were able to engage was largely attributable to the presence of similar existing research and clinical infrastructure[57]. As demonstrated by the collaboration between REMAP-CAP and CCA (see Box 1), leveraging existing research partnerships and relationships can be vitally important. This includes programs like the African coaLition [sic] for Epidemic Research, Response, and Training (ALERRT)[103] and the Pan-African Network for Rapid Research, Response, Relief, and Preparedness for Infectious Diseases Epidemics (PANDORA). Both programs are transnational research consortiums with clinical trial experience and established networks that were essential to the African response to COVID-19.

In many ways the sizable time and financial investment plus the longitudinal nature of many adaptive platform clinical trials can be synergistic with research capacity strengthening efforts. These types of trials are able to ensure the long-standing involvement of LMIC research staff and academic partners while also providing opportunities for gaining experience and expertise[10]. Because of the size and scope, large multi-national adaptive platform trial protocols and networks are well-positioned to "hibernate" during non-epidemic and -pandemic times but remain available for activation should conditions change[104]. These periods of latency are opportune for dedicated investment towards building research capacity and partnership equity that may be deprioritized during an acute pandemic response.

Discussion

Adaptive platform trials have risen to prominence globally in response to COVID-19, but their full potential, sustainability, and impact on LMIC research infrastructure remains to be seen. These trials have often been implemented by transnational research partnerships that bring an array of considerations rooted in power and global resource asymmetries between partners from LMICs and HICs drawing attention to particular equity-related opportunities and challenges.

We did not identify international research partnership equity challenges that are clearly unique to adaptive trials. However, there are many instances where the structure of these trials brings forward additional layers of complexity and acutely highlights existing asymmetries. This includes the perception that global scientific expertise in the design and conduct of these trials tends to be retained mostly in HIC settings resulting in research outputs that may not adequately adapt to LMIC-specific contexts. This structure of research partnership extends to access and availability of funding, regulatory oversight and leadership of these trials which, when missing key LMIC-specific input, risk perpetuating rather than dismantling existing global asymmetries. Finally, the structure

of data acquisition, analysis, and access in adaptive platform trials between multiple countries, settings, and interventions revisits a recurrent theme in global health research ethics: how to balance universal protocols with more context-specific needs of LMIC-based research participants and communities.

Opportunities in which adaptive platform trials may inform international research partnership equity standards include significant investment in LMIC clinical trial infrastructure that can be adapted to fit specific needs and interests of LMIC research communities. There is also the ability to capitalize on the need for REC familiarity with this type of trial design, which can occur concurrently in both HICs and LMICs through shared resources. Lastly, the flexibility of adaptive platform trial methods, including the addition or removal of study interventions based on temporal changes to the research or clinical environment, could pose justification for these trials in LMICs which face differing structural and resource limitations that can be underappreciated by HIC-based researchers and institutions.

We have presented eight themes that emerged from the literature and recent experience, but it is important to note that none of these topics occur as siloed entities from one another. There is significant overlap in many of the themes, for example between regulatory oversight and PTA when sponsors directly control the availability of interventions, data and biospecimens; or between research capacity building and essentially all of the other themes. Enhanced LMIC administrative, ethics, scientific, infrastructure, and institutional capacities would help support and inform LMIC representation in the other seven themes discussed.

Conclusions

The expanding use of multinational adaptive clinical trial designs into LMIC settings, particularly following globally relevant public health emergencies such as the COVID-19 pandemic and Ebola epidemic draws attention to several components of transnational research partnership equity that apply to global scientific research in general. Most notably this includes awareness of fairness and influence as it pertains to global concentration of knowledge acquisition and study design experience, balancing universal study protocols with pluralistic research community values and objectives, and the potential impact longitudinal, high-investment research studies can have on strengthening and sustaining LMIC research capacity. Adaptive platform trials provide a distinctive opportunity for further empirical investigation and practice innovation to begin to narrow some of the inequities that exist between LMIC and HIC collaborative partners engaged in global health research.

Reflexivity statement

J.A. and C.M. were the researchers approached by the WHO Ethics and Governance Unit to lead this project, which is one of five sub-aims discussed during the project group meeting in Geneva, Switzerland in July 2022. The authors of this manuscript are a combination of HIC- and LMIC-based researchers all of whom have experience working in LMIC/HIC international research collaborations, and with interrogating the ethics and regulatory dimensions of adaptive and alternative trial methods. LMIC-based authors G.C., W.N., and J.T. held the same roles and responsibilities as HIC-based authors J.S. and N.K., primarily providing critical feedback on preliminary and subsequent drafts of the manuscript.

Data availability

All data underlying the results are available as part of the article and no additional source data are required.

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Open Peer Review

Current Peer Review Status: ? ✓ ?

Version 2

Reviewer Report 11 December 2023

https://doi.org/10.21956/wellcomeopenres.22673.r70991

✓ **Thomas Nyirenda**
European and Developing Countries Clinical Trials Partnership, University of Stellenbosch Global Health Department, Cape Town, South Africa

I am happy with the authors' comments and amendments following my input.

Competing Interests: No competing interests were disclosed.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Version 1

Reviewer Report 14 August 2023

https://doi.org/10.21956/wellcomeopenres.20973.r62072

? **Peter van der Graaf**
Northumbria University, Newcastle upon Tyne, UK

A well written and thoughtful paper with a clear conclusion on applying equity principles in transnational partnerships from the perspective of low and middle-income countries when collaborating on adaptive platform trials. I enjoyed reading the paper.

The authors could strengthen the paper by adding more examples to each theme, particularly

around practical solutions suggested in response to identified challenges. It is also not always clear to me what the unique dimensions of the issues are highlighted under each theme for adaptive platform trial designs. The authors state that these challenges are heightened for this type of design, but do not always make clear in what ways.

For example, under the ethics oversight theme (page 8, 3rd paragraph), the authors argue that there is a need for more familiarity with adaptive platform trial designs among RECs and DMCs, including unique ethical considerations of these different methodologies. What are these ethical considerations and how are they unique?

Similarly, under the theme of regulatory oversight, (page 8, paragraph 5), the authors recommend re-evaluating processes for recognising the legitimacy of alternative regulatory frameworks. Can they give an example of such a framework? I appreciate they added a reference, but this does not give much insight; showing a brief practical example of how to apply an alternative framework to adaptive platform trials would be more helpful.

In the next paragraph, the authors identify a need for LMIC-specific guidance for internationally funded adaptive trials. What should this specific guidance look like and how will it differ from existing FDA and EMA guidance, as mentioned by the authors, to incorporate the experiences of regulatory bodies in LMICs?

Another example, when describing the challenges of post-trial access (PTA) to interventions, data, and specimens, the authors state that “providing PTA may be more realistic for some types of research interventions and partnerships than others” (page 9, 4th paragraph). What type of research interventions and partnerships are more amenable for PTA, given the challenges for LMIC partners to access this data?

I would also have liked to see a bit more detail on how the themes were developed. The authors briefly describe the process (triangulation of insights from the rapid narrative review with unpublished experiences and practices from meetings with project participants, and critical review by experts), but do not show how initial themes from the review were revised based on the meetings and expert reviews. It would be insightful to learn how the authors managed the blending of these different types of knowledge into the eight themes.

Two of the current themes appear to be more cross-cutting than the others and the authors might want to consider incorporating these themes in the other themes or making clearer the link between these two themes and the other ones.

For example, the knowledge translation theme seems to be dealing with the variation in interpretations of results through effective communication and preventing miscommunication. This is quite a limited take on knowledge translation with a focus on dissemination through appropriate language and products. However, the authors also mention the early involvement of key policy and practice stakeholders, which links to earlier suggestions in other themes to engage these groups in the trial design and conduct, which widens the scope of knowledge translational activities and makes it more a cross-cutting theme. (E.g., how to involve key stakeholders in all stages in response to issues identified under each theme to incorporate research results into local practice and cultural contexts?). This would also help to provide more clarity on the suggestion made by the authors at the end of this theme “to incorporate these uses into discussions about

policy and practice translations" How? (page 10, paragraph 2).

The second cross-cutting theme could be research capacity strengthening and maintenance. Building the research skills and experience of LMIC partners is mentioned in several of the other themes (for example, when developing epistemic structures and ethics oversight) and these suggestions could be linked together to illustrate the difference dimensions of capacity building required in transnational research partnerships for adaptive platform trial designs. What I feel is currently missing in this theme is a wider reflection on the capacity building needs for HIC researchers, as the current theme suggest that capacity building is particularly required for LMIC partners. How can HIC researchers be trained in getting a better understanding of LIMC needs, unique knowledge and local contexts, and upskilled in their understanding of adaptive platform trials to support transnational partnerships and ensure they are equitable?

I hope these suggestions are helpful and look forward to the authors' responses to my comments.

Is the work clearly and accurately presented and does it cite the current literature?
Yes

Is the study design appropriate and is the work technically sound?
Yes

Are sufficient details of methods and analysis provided to allow replication by others?
No

If applicable, is the statistical analysis and its interpretation appropriate?
Not applicable

Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Public Health, Knowledge Mobilisation, Collaborative Research Partnerships

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 11 Nov 2023

Chelsea Modlin

Thank you for the opportunity to submit a revised version of the manuscript **"Towards achieving transnational research partnership equity: lessons from implementing**

adaptive platform trials in low- and middle-income countries" (manuscript 18915) . We appreciate the time and attention dedicated to improving the manuscript and have incorporated the suggestions made by the reviewer. Please see below for a point-by-point response to the reviewer comments.

Comment 1: The authors could strengthen the paper by adding more examples to each theme, particularly around practical solutions suggested in response to identified challenges. It is also not always clear to me what the unique dimensions of the issues are highlighted under each theme for adaptive platform trial designs. The authors state that these challenges are heightened for this type of design, but do not always make clear in what ways. For example, under the ethics oversight theme (page 8, 3rd paragraph), the authors argue that there is a need for more familiarity with adaptive platform trial designs among RECs and DMCs, including unique ethical considerations of these different methodologies. What are these ethical considerations and how are they unique?
Response: We appreciate the focus on this issue and will reference back to the response to Reviewer 2 Comment 4 as the ethical considerations unique to adaptive platform trials was explored in detail within another paper included in the same series as our manuscript.

Comment 2: Similarly, under the theme of regulatory oversight, (page 8, paragraph 5), the authors recommend re-evaluating processes for recognising the legitimacy of alternative regulatory frameworks. Can they give an example of such a framework? I appreciate they added a reference, but this does not give much insight; showing a brief practical example of how to apply an alternative framework to adaptive platform trials would be more helpful.
Response: This is a great point. For the sake of word count consolidation and to avoid redundancy with work that was completed by others within the broader project, we have added a reference to where readers can find a more detailed discussion of current and alternative regulatory frameworks for adaptive platform trials (doi.org/10.12688/wellcomeopenres.19058.1). Page 15, Paragraph 1: "A more detailed discussion of regulatory considerations for adaptive platform trials can be found in another article in this series (84)."

Comment 3: In the next paragraph, the authors identify a need for LMIC-specific guidance for internationally funded adaptive trials. What should this specific guidance look like and how will it differ from existing FDA and EMA guidance, as mentioned by the authors, to incorporate the experiences of regulatory bodies in LMICs?
Response: The suggestion raised here is also important and aligned with the purpose of our manuscript compared to the reference cited in the response to Comment 2. We have added the following text to serve as one hypothetical example given a dearth of real-world examples within the published literature. Follow up work qualitatively describing these types of details within multinational adaptive platform design trials in LMICs during COVID-19 is one of the projects that is currently being planned as a result of this preliminary work. Pages 15, Paragraph 1: "In addition, although basic regulatory and design requirements for clinical trials using adaptive methods are available from the U.S. Food and Drug Administration (FDA) (82) and the European Medicines Agency (EMA) (83), these are recommendations based on experiences and regulatory bodies situated in HICs. For example, the FDA report Adaptive Designs for Clinical Trials of Drugs and Biologics Guidance for Industry (82) details the complexities of planning for simulations to reduce

statistical errors that are specific to potential components of adaptive platform trials such as adaptations to treatment arm interventions or evolving endpoints. It is possible that expertise in these advanced statistical methods is limited in LMICs and other under-resourced areas and there is no formal guidance for how to develop this skill set where it did not previously exist, leaving it up to the discretion of individuals partnerships. While this may not necessarily be within the scope of the FDA to determine, special regulatory considerations for internationally funded adaptive trials conducted in LMICs, and LMIC-specific guidance for these trials, including capacity development recommendations or requirements, is needed."

Comment 4: Another example, when describing the challenges of post-trial access (PTA) to interventions, data, and specimens, the authors state that "providing PTA may be more realistic for some types of research interventions and partnerships than others" (page 9, 4th paragraph). What type of research interventions and partnerships are more amenable for PTA, given the challenges for LMIC partners to access this data?
Response: We have added an example to the text specific to COVID-19 multinational adaptive trials based on the discussion that was held with the REMAP-CAP group. Page 16-17, Paragraph 1: "In adaptive platform clinical trials, PTA to successful study-related interventions and biospecimens can be complicated by the dynamic nature of the research design as the final intervention or research population is not always the same as when the trial started. COVID-19 adaptive platform trials included widely-available therapeutics (e.g., aspirin) and novel therapeutics (e.g., monoclonal antibodies) at various points of time during the pandemic. Due to a combination of limited global availability and stipulations of the pharmaceutical companies sponsoring these trials, it was often not realistic to expect novel therapeutics to be available post-trial in LMICs (9). Intervention arms therefore focused on treatment options that would be locally feasible to implement, which were often repurposed medications."

Comment 5: I would also have liked to see a bit more detail on how the themes were developed. The authors briefly describe the process (triangulation of insights from the rapid narrative review with unpublished experiences and practices from meetings with project participants, and critical review by experts), but do not show how initial themes from the review were revised based on the meetings and expert reviews. It would be insightful to learn how the authors managed the blending of these different types of knowledge into the eight themes.
Response: We have addended the methods to include more detail as suggested by the reviewer. Page 10 , Paragraph 3: "Notes taken from this meeting were integrated into the working themes identified from the literature reviews (including areas of congruence and conflict), discussed between the authors until consensus was reached, and a preliminary report was drafted. This report was then discussed during a project group meeting in Geneva, Switzerland in July 2022. Findings were iteratively revised based on the discussion and feedback from this meeting, including areas relevant to the scope of this report compared to other aims of the project, and from critical review by experts in ethics, global health, and adaptive clinical trial methods who provided staged feedback on preliminary drafts of this report."

Comment 6: Two of the current themes appear to be more cross-cutting than the others

and the authors might want to consider incorporating these themes in the other themes or making clearer the link between these two themes and the other ones. For example, the knowledge translation theme seems to be dealing with the variation in interpretations of results through effective communication and preventing miscommunication. This is quite a limited take on knowledge translation with a focus on dissemination through appropriate language and products. However, the authors also mention the early involvement of key policy and practice stakeholders, which links to earlier suggestions in other themes to engage these groups in the trial design and conduct, which widens the scope of knowledge translational activities and makes it more a cross-cutting theme. (E.g., how to involve key stakeholders in all stages in response to issues identified under each theme to incorporate research results into local practice and cultural contexts?). This would also help to provide more clarity on the suggestion made by the authors at the end of this theme "to incorporate these uses into discussions about policy and practice translations" How? (page 10, paragraph 2).
Response: The is an important point and one of the inherent challenges within the international research partnership equity space, namely that many of these themes overlap, or sometimes even contradict, one another depending on the specific context they are being applied to. We have renamed this theme 'Knowledge Translation and Dissemination' in an attempt to distinguish that here we primarily focus on the transformation of scientific knowledge generated by a research partnership to both the local community and scientific community at large. We have also added the following text to the Discussion section to help point out that none of these themes should be treated as siloed from one another given the dynamic and often individualized approach required to meet certain equity strengths, limitations, and goals within a research partnership, geographic setting, research focus, etc. Page 17, Paragraph 3: "Issues like these differences need to be incorporated into discussions about policy and practice translation by inviting pluralistic analyses and interpretations of research data and conclusions. It is particularly important to include those with expertise in local contexts, and what these differences would mean in terms of health policy actions taken in response to this new scientific knowledge. Doing so requires a firm foundational knowledge of how trials are designed and associated limitations of specific methodologies." Page 19, Paragraph 4: "We have presented eight themes that emerged from the literature and recent experience, but it is important to note that none of these topics occur as siloed entities from one another. There is significant overlap in many of the themes, for example between regulatory oversight and PTA when sponsors directly control the availability of interventions, data and biospecimens; or between research capacity building and essentially all of the other themes. Enhanced LMIC administrative, ethics, scientific, infrastructure, and institutional capacities would help support and inform LMIC representation in the other seven themes discussed."

Comment 7: The second cross-cutting theme could be research capacity strengthening and maintenance. Building the research skills and experience of LMIC partners is mentioned in several of the other themes (for example, when developing epistemic structures and ethics oversight) and these suggestions could be linked together to illustrate the difference dimensions of capacity building required in transnational research partnerships for adaptive platform trial designs. What I feel is currently missing in this theme is a wider reflection on the capacity building needs for HIC researchers, as the current theme suggest that capacity building is particularly required for LMIC partners. How can HIC researchers

be trained in getting a better understanding of LIMC needs, unique knowledge and local contexts, and upskilled in their understanding of adaptive platform trials to support transnational partnerships and ensure they are equitable?
Response: This is a very key point. We have addressed the bilateral nature of capacity building with the following text and have also added text to the Discussion section mentioned in Comment 6 to highlight that these themes intersect with one another. Page 18, Paragraph 1: "...focusing research capacity efforts on the LMIC partners. This does not preclude the importance of HIC capacity building, particularly in understanding LMIC contexts and needs as well as evaluating internal power dynamics to determine how HIC-based institutions, researchers, and sponsors can initiate or transition into positions of allyship instead of leadership." We greatly appreciate the careful consideration of our work and thank the reviewer for offering the opportunity to strengthen the manuscript based on these helpful comments.

Competing Interests: No competing interests were disclosed.

Reviewer Report 02 August 2023

https://doi.org/10.21956/wellcomeopenres.20973.r59883

?

Thomas Nyirenda
European and Developing Countries Clinical Trials Partnership, University of Stellenbosch Global Health Department, Cape Town, South Africa

1. There is a generalisation that adaptive trial platforms were poorly understood before COVID-19 pandemic. These platforms have been used in NCD research especially in Cancer. PANACEA (PanACEA (panacea-tb.net)) infectious disease (TB) research consortium funded by EDCTP has also been in existence since 2007. These two aspects are worth mentioning in the paper.

2. In relation to PANACEA one of the lessons that be requested for sharing from them are lessons (if any) around challenges of transferring leadership from the scientists in the north to those in the south during the course of long research programs

3. Under ethics one of the recent projects worth mentioning is the PREPARED which aims to build global consensus in making research during crises ethical (PREPARED (prepared-project.eu)

4. Adaptive trial designs are indeed very complex and risk wastage of invested money and time if they end up being poorly designed and fail to answer the questions they were designed to address. The risk rises as during the course of the trials endpoints constantly

change too. The Bill and Melinda Gates Foundation have funded a Design, Analyse and Communicate Programme (recently launched in Africa in Cameroon as its host country) - Welcome • DAC Trials (tghn.org). This great initiative deserves a mention in the paper for the quality and efficiency reasons mentioned.

Is the work clearly and accurately presented and does it cite the current literature?
Partly

Is the study design appropriate and is the work technically sound?
Yes

Are sufficient details of methods and analysis provided to allow replication by others?
Yes

If applicable, is the statistical analysis and its interpretation appropriate?
Not applicable

Are all the source data underlying the results available to ensure full reproducibility?
No source data required

Are the conclusions drawn adequately supported by the results?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Clinical research/ trials and capacity development

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 11 Nov 2023

Chelsea Modlin

Thank you for the opportunity to submit a revised version of the manuscript **"Towards achieving transnational research partnership equity: lessons from implementing adaptive platform trials in low- and middle-income countries"** (manuscript 18915). We appreciate the time and attention dedicated to improving the manuscript and have incorporated the suggestions made by the reviewer. Please see below for a point-by-point response to the reviewer comments.

Comment 1: There is a generalisation that adaptive trial platforms were poorly understood before COVID-19 pandemic. These platforms have been used in NCD research especially in Cancer. PANACEA (PanACEA (panacea-tb.net)) infectious disease (TB) research consortium funded by EDCTP has also been in existence since 2007. These two aspects are worth mentioning in the paper.

Response: We appreciate the review's insights into this topic and have added the suggested resources into the introduction of the manuscript which is also linked to the PanACEA website for reference. Page 4, Paragraph 1: "These types of trial design were already familiar to some endemic infectious disease research (e.g., the PanACEA tuberculosis trials) and non-communicable diseases research, particularly in oncology. However, increased attention to adaptive platform trials arose in response to recent global infectious epidemics and pandemics."

Comment 2: In relation to PANACEA one of the lessons that be requested for sharing from them are lessons (if any) around challenges of transferring leadership from the scientists in the north to those in the south during the course of long research programs.
Response: Thank you for this note – the transfer of leadership from HICs to LMICs is a component of leadership considerations and power differentials within international research partnerships. We have added the following text to highlight this issue although our review of adaptive platform trials did not specifically identify this theme. It suggests the importance of further qualitative investigation with researchers who participate in multinational adaptive platform trials to elucidate how this consideration transferred to adaptive trials specifically. Page 15, Paragraph 2: "For longitudinal research programs, the transfer of leadership from HIC- to LMIC-based researchers is often advocated for but can, in reality, sometimes be hindered by institutional and individual-level factors. But this is not always the case and there are many examples of partnerships that have enacted very intentional efforts in the training of LMIC leaders and transfer of partnership responsibilities."

Comment 3: Under ethics one of the recent projects worth mentioning is the PREPARED which aims to build global consensus in making research during crises ethical (PREPARED (prepared-project.eu
Response: This suggestion has been added to the 'Ethics Oversight' row under 'Potential Solutions' in Table 2 with a link to the PREPARED initiative website for reference. Table 2: "Ethical oversight during public health emergencies that goes beyond IRBs is also developing, including efforts such as the PREPARED initiative."

Comment 4: Adaptive trial designs are indeed very complex and risk wastage of invested money and time if they end up being poorly designed and fail to answer the questions they were designed to address. The risk rises as during the course of the trials endpoints constantly change too. The Bill and Melinda Gates Foundation have funded a Design, Analyse and Communicate Programme (recently launched in Africa in Cameroon as its host country) - Welcome • DAC Trials (tghn.org). This great initiative deserves a mention in the paper for the quality and efficiency reasons mentioned.
Response: This is a very relevant consideration on the ethical management of adaptive platform trials especially as there is debate as to whether the cost of adaptive trials exceeds that of large-scale fixed trial designs. It overlaps with the discussion in the paper "Adaptive clinical trials in public health emergency contexts: ethics considerations" (doi.org/10.12688/wellcomeopenres.19057.1) which is a part of the same series as our manuscript. We have added the following text to help highlight the connection between the two papers: Page 14, Paragraph 1: "Another article in this series provides additional analyses of the ethical considerations unique to adaptive platform trials (75)." We greatly

appreciate the careful consideration of our work and thank the reviewer for offering the opportunity to strengthen the manuscript based on these helpful comments.

Competing Interests: No competing interests were disclosed.

Reviewer Report 02 August 2023

https://doi.org/10.21956/wellcomeopenres.20973.r59891

?

Justin Pulford
Liverpool School of Tropical Medicine, Liverpool, UK

This paper presents a synthesis of equity issues common to transnational research partnerships and then examines these issues from the point of view of adaptive platform trials. Potential solutions to addressing identified inequities, especially opportunities where adaptive platform trials may be especially well suited to addressing inequities, are identified. Suggested amendments to the paper include:

Introduction

Given the focus on equity, it would be helpful to include a working definition somewhere in the introduction.

Amend the sentence: 'We offer a thematic analysis of eight areas where asymmetries exist…' to 'We offer a thematic analysis of eight areas where asymmetries **can** exist…'

Methods

While I recognise the authors employed both 'rapid' and 'selective' reviews, it would still be informative to understand how much literature was identified and subsequently utilised (and what type of literature etc). The authors could consider reporting selected PRISMA criteria as appropriate.

The list of publications subsequently included in both reviews could be presented as a supplementary file.

Given the focus on equity, it would be useful to include some description of the authors' LMIC representation and North-South research partnership experience in the methods.

Results

There is a lot of content under each theme and it is not always presented in a consistent way across themes. In general, there seems to be an overview of challenges related to the theme, some proposed solutions that are not necessarily specific to adaptive platform trials and then considerations/recommendations that are specific to adaptive platform trails. In some cases an example is presented, in some cases not. I would suggest employing a consistent format throughout and include (consistent) sub-headings. The text under each theme is quite lengthy, so consideration could be given to the use of a Table, e.g. Each theme could begin with a description of the equity issues identified and then proposed solutions (both general and adaptive platform specific) could be presented in an overarching (covering all 8 themes) table. This would make it easier to follow and would better highlight the adaptive platform-specific content.

Where recommendations are made, it is not always clear who the intended audience is. This needs to be made clearer. If you adopt the tabular approach suggested above, then against each stated recommendation you could identify the intended audience/s.

Conclusion

If the authors reduce text in the 'results' section as suggested, then this would create word space for a more traditional 'discussion then conclusion' format. I suggest this as the current conclusion touches on two key discussion points that warrant a stronger connection with the equity literature: 1) equity issues that appear common across research methodologies; and 2) equity issues that are especially pertinent in an adaptive platform trial context. The latter, in particular, warrants elaboration as this is a key contribution of the paper, i.e. what common equity issues are adaptive platform trials especially well placed to address, who should take responsibility and how.

Is the work clearly and accurately presented and does it cite the current literature?
Yes

Is the study design appropriate and is the work technically sound?
Yes

Are sufficient details of methods and analysis provided to allow replication by others?
Partly

If applicable, is the statistical analysis and its interpretation appropriate?
Not applicable

Are all the source data underlying the results available to ensure full reproducibility?
Partly

Are the conclusions drawn adequately supported by the results?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Research capacity strengthening theory, methods and evaluation

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 11 Nov 2023

Chelsea Modlin

Thank you for the opportunity to submit a revised version of the manuscript **"Towards achieving transnational research partnership equity: lessons from implementing adaptive platform trials in low- and middle-income countries"** (manuscript 18915). We appreciate the time and attention dedicated to improving the manuscript and have incorporated the suggestions made by the reviewer. Please see below for a point-by-point response to the reviewer comments.

Comment 1: Given the focus on equity, it would be helpful to include a working definition somewhere in the introduction.
Response: Thank you for the suggestion. We have added a definition of research partnership equity to the introduction. Page 4, Paragraph 2: "We define "research partnership equity" as collaborative and inclusive research practices that incorporate fairness of opportunity and prioritize mutually beneficial inputs, processes, outputs, and impact."

Comment 2: Amend the sentence: 'We offer a thematic analysis of eight areas where asymmetries exist…' to 'We offer a thematic analysis of eight areas where asymmetries **can** exist…'
Response: This has been revised. Page 6, Paragraph 3: "We offer a thematic analysis of eight areas where asymmetries can exist within transnational research partnerships…"

Comment 3: While I recognise the authors employed both 'rapid' and 'selective' reviews, it would still be informative to understand how much literature was identified and subsequently utilised (and what type of literature etc). The authors could consider reporting selected PRISMA criteria as appropriate.
Response: We appreciate the response and do recognize the importance of systematic literature review to decrease the risk of bias within the analysis. We have revised the methods section to include the inclusion criteria utilized and added limitations, including how this may have impacted our conclusions and replicability. Page 10, Paragraphs 1 & 2: "We performed a rapid narrative review (49) on transnational research partnership equity, which was cross-referenced with selective reviews of literature on adaptive clinical trial designs and adaptive platform designs, including those reporting COVID-19 and Ebola research in order the answer the following question: What transnational research partnership equity considerations are relevant to adaptive platform clinical trials? This approach allowed for broad examination of emerging evidence, evaluation for more specific lines of inquiry, clarification of concepts, and synthesis of two largely separate, but converging lines of published literature. PubMed/MEDLINE, Scopus, and Google Scholar databases were reviewed in March and revisited in May of 2022 using keyword searches for 'equity' OR 'fairness' AND 'international research partnerships' OR 'global research

partnerships' 'OR 'transnational research partnerships' OR 'North-South partnerships.' Eligibility criteria included postings that 1.) describing or categorizing the components of international research partnership equity; 2.) were peer-reviewed and featured primary empirical research, published guidelines or policies, program reports, normative/conceptual articles, or commentaries/editorials; and 3.) published in English. There were no publication date specifications. The selective literature search on adaptive clinical trials focused on ethical analyses and operationalization of these trials and included search terms 'adaptive clinical trial +/- designs' OR 'platform trial' AND 'ethics' OR 'ethical considerations' OR 'experience' OR 'operationalization' OR 'implementation.' Eligibility criteria were identical to those listed above. The citations were appraised and relevant postings were included in subsequent abstract and full-text reviews. Searches were conducted by two independent reviewers who met to discuss findings and develop and apply thematic categorizations. Any variation in interpretation or classification of findings was resolved by consensus. Because of the limited project timeframe, further systematic tracking of the literature aside was not pursued. One of the limitations of this approach is that we cannot exclude any potential bias introduced from an informal review as opposed to using a more formal approach, perhaps limiting the replicability of our findings. Additionally, the definition and components of research partnership equity are evolving over time complicating literature identification.

Comment 4: The list of publications subsequently included in both reviews could be presented as a supplementary file.
Response: Please see response to Comment 3.

Comment 5: Given the focus on equity, it would be useful to include some description of the authors' LMIC representation and North-South research partnership experience in the methods.
Response: We have included the suggested description but included this as a reflexivity statement. Page 19, Paragraph 2: "J.A. and C.M. were the researchers approached by the WHO Ethics and Governance Unit to lead this project, which is one of five sub-aims discussed during the project group meeting in Geneva, Switzerland in July 2022. The authors of this manuscript are a combination of HIC- and LMIC-based researchers all of whom have experience working in LMIC/HIC international research collaborations, and with interrogating the ethics and regulatory dimensions of adaptive and alternative trial methods. LMIC-based authors G.C., W.N., and J.T. held the same roles and responsibilities as HIC-based authors J.S. and N.K., primarily providing critical feedback on preliminary and subsequent drafts of the manuscript."

Comment 6: There is a lot of content under each theme and it is not always presented in a consistent way across themes. In general, there seems to be an overview of challenges related to the theme, some proposed solutions that are not necessarily specific to adaptive platform trials and then considerations/recommendations that are specific to adaptive platform trails. In some cases an example is presented, in some cases not. I would suggest employing a consistent format throughout and include (consistent) sub-headings. The text under each theme is quite lengthy, so consideration could be given to the use of a Table, e.g. Each theme could begin with a description of the equity issues identified and then proposed solutions (both general and adaptive platform specific) could be presented in an overarching (covering all 8 themes) table. This would make it easier to follow and would

better highlight the adaptive platform-specific content.
Response: Following the reviewer's suggestion we have substantially revised the manuscript format and Table 2. Each of the eight themes is now in sections with headings 'Challenges' (general to international research partnerships) and 'Considerations for Adaptive Platform Trials'. In-depth examples from the text have been moved to separate boxes to help distinguish these from the main text. Suggested solutions from the literature review have been moved to an expanded version of Table 2.

Comment 7: Where recommendations are made, it is not always clear who the intended audience is. This needs to be made clearer. If you adopt the tabular approach suggested above, then against each stated recommendation you could identify the intended audience/s.
Response: Thank you for pointing this out. We have updated the text to reflect the intended audience identified for the project. Page 10, Paragraph 1: "The intended audiences of this project are researchers, institutions, funders and sponsors who currently or plan to engage in multinational adaptive platform clinical trials."

Comment 8: If the authors reduce text in the 'results' section as suggested, then this would create word space for a more traditional 'discussion then conclusion' format. I suggest this as the current conclusion touches on two key discussion points that warrant a stronger connection with the equity literature: 1) equity issues that appear common across research methodologies; and 2) equity issues that are especially pertinent in an adaptive platform trial context. The latter, in particular, warrants elaboration as this is a key contribution of the paper, i.e. what common equity issues are adaptive platform trials especially well placed to address, who should take responsibility and how.
Response: The suggested revisions have been made, including changing the 'Findings' section to 'Results' and including a short 'Discussion' section to summarize how adaptive platform trials can help inform international research partnership equity. This was kept relatively brief to avoid redundancy with the information reviewed in the results section which includes more detail. We greatly appreciate the careful consideration of our work and thank the reviewer for offering the opportunity to strengthen the manuscript based on these helpful comments.

Competing Interests: No competing interests were disclosed.