












Ethical priorities for international collaborative adaptive platform trials for public health emergencies

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INTRODUCTION: THE PROMISE OF ADAPTIVE TRIAL DESIGNS

Public health emergencies caused by new or re-emerging infectious diseases demand urgent answers regarding effective medical countermeasures. In past pandemics, standard trial designs proved unable to produce results in time to support effective response.¹ Adaptive platform trials, using a master protocol across numerous sites, multiple intervention arms and adaptive methodologies, offer a promising design solution. Several such trials, including RECOVERY, Solidarity, PRINCIPLE and REMAP-CAP, played a significant role in the global research response to COVID-19. Their size and their flexible ability to add and remove arms in response to emerging information helped generate rapid evidence on the effectiveness of both repurposed and novel interventions for COVID-19, and saved many lives. Importantly, they also generated rapid evidence to show some widely-used interventions were not effective, limiting harm to patients and unnecessary costs to health systems.²

Emergency preparedness, in the form of well-established networks able to pivot to emergency research, was essential to the success of these trials. Substantial investments in these networks before the COVID-19 pandemic paid significant dividends. Research teams with years of experience working together across multiple sites and countries had substantial advantages over those obliged to start from scratch.

Investment in 'ethical preparedness' similarly paid dividends, with some countries developing emergency guidelines and procedures in light of their experiences with Ebola and Zika.³ WHO,⁴ PAHO⁵ and the research network ALERRT,⁶ among others, supported dialogue and produced ethics guidance,

SUMMARY BOX

- ⇒ Rapidly produced evidence on effective medical counter measures is critical for responding to health emergencies caused by (re-)emerging infectious diseases.
- ⇒ Adaptive platform trials played a significant role in the global research response to COVID-19 and are likely to be increasingly used in the future, both in emergency and non-emergency contexts.
- ⇒ We call attention to a number of ethical considerations that should influence the development and future implementation of large-scale multicountry adaptive platform studies.

alongside decades of investment by the National Institutes of Health Fogarty International Center supporting ethics capacity strengthening in low-income and middle-income countries (LMICs). This provided a sound basis for rapid ethical support for COVID-19 researchers: WHO produced timely guidance on many ethically challenging aspects of COVID-19 research and provided valued opportunities to share knowledge and experience through the Epidemics Ethics platform.⁷

LOOKING TO THE FUTURE

In September 2022, the World Health Assembly (WHA) approved a Resolution on 'strengthening clinical trials to provide high-quality evidence on health interventions and to improve research quality and coordination'.⁸ The resolution reiterated the central role of well-designed and ethically conducted trials in ensuring the safety and efficacy of health interventions, in both normal times and emergencies. It highlighted the role of clinical trial networks, developed

Box 1 Priority research questions to help inform equitable, person-centred research practice

- ⇒ What can be learnt from the COVID-19 adaptive platform studies that would help strengthen the integration of ethics in an ongoing manner into project management processes?
- ⇒ How can researchers, public health officials, communities and other key stakeholders in LMICs be meaningfully involved in planning and rolling out adaptive platform trials to ensure equitable partnerships?
- ⇒ What were the barriers and enablers for good participatory practice (GPP) in the major COVID-19 adaptive platform studies, and how might this inform revised guidance on what GPP looks like in the context of platform adaptive trials?
- ⇒ How can researchers be supported and encouraged to document and report on the experience and outcomes of community engagement, so that practice can be strengthened?
- ⇒ What information is appropriate to communicate to participants on adaptive features of trials to support informed consent, and how can such information be shared effectively, including during an infectious disease outbreak?
- ⇒ What were the challenges and experiences of research ethics committees and data safety and monitoring boards in reviewing protocols and data for adaptive platform studies during COVID-19, and how could committees be better supported in future?
- ⇒ What evidence is there of benefit to less well-resourced countries from involvement in adaptive platform trials, including changed medical practice, improved health outcomes or strengthened research capacity?

LMICs: low-income and middle-income countries.

in collaboration with local populations, and the need for flexible and responsive oversight and regulatory systems.

Undoubtedly, new infectious disease outbreaks will emerge, with the associated need for rapid research to identify countermeasures. The success of adaptive platform trial designs in responding to COVID-19, and the endorsement by the WHA of major clinical trial networks, highlights the need to review experience to date so that trials can be conducted even quicker and better in future emergencies: driven by scientific rigour, and underpinned by sound ethical practice. Drawing on five reviews commissioned by the WHO Health Ethics and Governance Unit,^{2 9–12} that subsequently formed the basis for an expert round table held in Geneva in July 2022, we offer the following ethics-related key considerations to support the further development of international collaborative adaptive platform trials. Priority questions for future research and practice identified at the round table are set out in [box 1](#). Further analysis and considerations from individual authors are found in the five published reviews.

AN EQUITABLE APPROACH TO EMERGENCY PREPAREDNESS

The investment, infrastructure and collaboration required to support adaptive platform trials in delivering the benefits of rapid evidence generation is significant. The equitable distribution of resources necessary to plan and operationalise trials, and consequently translate the trial benefits themselves, is a key concern, particularly

if large-scale approaches are prioritised in future trial funding portfolios. Funders need to be alert to the world regions that are currently less involved in global trial networks and hence risk being excluded—both from opportunities to develop their research capacity and from determining research priorities relevant to their needs.

All stakeholders also need to be alert to the values and vision embedded in the leadership of those networks. Most adaptive platform trials, to date, have been led from high-income countries. Moving forward, it is crucial to ensure that questions of equity and power dynamics, between and within the institutions and countries involved in these networks, are given serious attention from the beginning. A particular focus on decision-making structures that facilitate equitable input from all partners, and the resulting ownership of rapid evidence generation in LMICs, is needed to find solutions that meet specific needs and contexts.

ETHICS IN THE NUTS AND BOLTS OF PROCESS MANAGEMENT AND EVIDENCE INTO PRACTICE

Ethics considerations are inherent in the decisions made throughout every aspect of clinical research: when it is conceived, funded, planned, reviewed, implemented and disseminated. Research ethics committees provide independent review of some of these decisions. However, such safeguards do not, in themselves, make research practice ethical.

The effective management of research, from the launch of well-designed studies with the minimum of delay, to the prompt translation of knowledge and uptake of findings into policy and practice, is itself a matter of ethical concern. COVID-19 platform studies demonstrated how rapidly and effectively this could be achieved—and the associated value to patients in many parts of the world in improved and cost-effective care.² Further analysis of the experience of such studies—understanding what contributed to ethically informed timely evidence generation, knowledge translation and uptake, and what did not—is crucial for achieving further future gains in effective emergency response.

IMPLICATIONS FOR GOOD PARTICIPATORY PRACTICE

Strong communication and engagement practices are key to ethical, acceptable and relevant implementation of trials. WHO's Good Participatory Practice (GPP) provides a supportive framework for advancing these capabilities.¹³ Some aspects of platform trials, including the way that they can support long-term research activity in one locality, may be particularly conducive to GPP, enabling long-term relationships to be formed. Other features, relating to the nature of the 'platform' and the scope for adaptation, raise new considerations (see [box 2](#)).

While, anecdotally, many COVID-19 research teams found ways to incorporate community perspectives into their studies despite extreme time pressures, there is little formal documentation of these experiences. We

Box 2 Features of adaptive platform trials relevant to good participatory practice (GPP)

- ⇒ Local adaptation: What aspects of the trial procedures must be consistent across all sites, and which can be adapted locally to ensure research is conducted as per protocol, yet in accordance with local norms and requirements?
- ⇒ Readiness: What constitutes appropriate engagement regarding readiness for clinical research participation during inter-pandemic periods? For example, in assessing questions such as acceptability and social value of clinical trials before an emergency occurs?
- ⇒ Engagement: What constitutes good, rapid engagement across the many sites involved before an adaptive trial begins, particularly in the context of an emergency?
- ⇒ Key junctures: During a trial, what are the key junctures of adaptive platform trials at which GPP can inform trial progression, for example, as the landscape of possible licensed treatments and vaccines evolves, and new arms are added?

need to understand how GPP was rapidly implemented; what the enabling factors were for good practice; and what barriers can be identified and overcome to promote good practice in future events.

TAKING A PERSON-CENTRED APPROACH TO CONSENT

More research is needed in advance of future emergencies to understand better what people—from many different contexts and cultures—want and need to know about adaptive platform studies before they provide (or refuse) informed consent to participate. Approaches to consent for these kinds of trials need to recognise the insecurity people may feel taking part in research in an emergency, and how this insecurity may be exacerbated by the new approach to research inherent in adaptive methodologies. More information and longer consent forms are almost certainly not the answer. Rather, we need to learn from the experiences and perspectives of participants in COVID-19 studies and build on existing work exploring creative ways to explain both traditional and novel design concepts.

TROUBLESHOOTING IN ETHICS REVIEW AND TRIAL MONITORING

Research ethics committees have struggled at times with the complexity and novel ethical questions raised by adaptive design methodologies.⁹ This raises specific questions of capacity strengthening, separate from existing well-recognised resourcing and capacity issues for ethical review systems in many parts of the world. Committee members need access to high-quality training resources to gain confidence in dealing with adaptive methodologies and the complexities of master protocols that will be implemented across multiple sites. Equally, researchers need to take responsibility for explaining their trial proposals clearly. More widely, the particular

complexities of reviewing adaptive platform trials point to a longer-term need to develop more flexible and dynamic models of review, including the role of trial monitoring. What is the role of data and safety monitoring committees in the context of trials where monitoring is occurring on an ongoing basis as a feature of the trial protocol?

CONCLUSION

Large-scale adaptive platform trials, conducted by international research networks, are likely to play an increasingly important role in both emergency and non-emergency research. Funding such major networks inevitably involves opportunity costs—for other kinds of research, and for research institutions not involved in those networks. Here, and in the five WHO-commissioned reviews,^{2 9–12} we draw attention to how all parts of the research ecosystem need to keep in view these key ethical questions of power, equity and respect for local contexts and needs, as they take forward these effective models of research.

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