Ethics and adaptive platform trial design in public health emergencies

Meeting report
18–19 July 2022, Geneva, Switzerland
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Acknowledgements

This document presents a summary report of a two-day meeting on Ethics and adaptive platform trial design in public health emergencies organized by the World Health Organization (WHO) on 18-19 July 2022.

The meeting was led by Katherine Littler (Co-Unit Head of the Health Ethics and Governance Unit in the WHO Department of Research for Health), under the overall guidance of John Reeder (Director, the Department of Research for Health). Katharine Wright (Consultant, United Kingdom) was the lead writer.

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1. Overview

Platform trials using adaptive methods have played a key role in the research response to COVID-19. They raise important ethical issues, however, associated not only with the methods used but also with their scale, their global nature and their probable contribution to pandemic preparedness. This report summarizes the discussions at a 2-day meeting on the findings of five rapid reviews on the ethical aspects of adaptive platform trials after the first 2 years of the COVID-19 pandemic. Cross-cutting themes included the importance of “lean” project management and of pre-pandemic preparedness, particularly in forming trusted relationships in international networks; challenges to meaningful community engagement, ethics review and participant consent; questions of inclusion and the implications for equitable access; factors that influence the fairness and sustainability of international partnerships, including capacity development and knowledge transfer; and governance arrangements that ensure both local and global accountability. Remaining evidence gaps were identified.
2. Introduction

Adaptive trial methods used in multi-site platform clinical trials have played an important role in the research response to the COVID-19 pandemic. Although only a very small proportion of COVID-related studies to date have been conducted with an adaptive platform design, these studies (including Solidarity, RECOVERY, PRINCIPLE and REMAP-CAP) involved recruitment of large numbers of participants and have provided rapid evidence on both repurposed and novel therapeutics for COVID-19. With over 135,000 participants recruited to six major platform trials and funding of over US$ 100 million, they have not only saved many lives but have also provided evidence that a number of widely used interventions were not effective, thus helping to preserve health-care resources and protect patient safety.

These methods are relatively new and potentially raise a number of ethical and governance challenges, affecting a wide variety of research stakeholders. In order better to understand and respond to these challenges, the Health Ethics and Governance Unit of WHO commissioned five rapid reviews, on: the role and policy impact of adaptive platform trials during COVID-19; ethical challenges associated with technical aspects of adaptive design; implications for consent and public engagement; impact on equity in transnational partnerships; and implications for governance and oversight (see Annex 2 for details of each review). The meeting brought together the lead authors of the five reviews and WHO staff to explore common themes, to identify areas in which further empirical research is required and to determine whether additional ethical guidance might be useful for research stakeholders.

This report summarizes the key themes that emerged from the review presentations and the subsequent discussion. The detailed reports of the five reviews are available separately, and the participants are listed in Annex 1. Annex 3 lists empirical research questions identified during the meeting as important for promoting and supporting best practice in future adaptive platform trials.

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Definitions

Adaptive clinical trial: There is no single definition of adaptive study design. The definitions drawn on by contributors to the meeting included: “a clinical trial design that incorporates the possibility of modifying some aspect of the trial while it is still ongoing based on data collected in the trial”7 and “a design that allows modifications to be made to a trial’s design or statistical procedures during its conduct, with the purpose of efficiently identifying clinical benefits/risks of new drugs or to increase the probability of success of clinical development”.8 The US Food and Drug Administration defines an adaptive design as a “clinical trial design that allows for prospectively planned modifications to one or more aspects of the design based on accumulating data from subjects in the trial.”9

Platform clinical trials: Contributors drew on the definition of platform clinical trials given in a 2022 rapid review of (self-identified) platform trials during the COVID-19 pandemic:

“[Platform trials] are considered a type of master protocol, which provides an overarching protocol designed to answer multiple questions; platform protocols adaptively allow for experimental therapies to enter or leave the trial over the course of the trial. The simultaneous assessment of multiple experimental therapies under a single protocol offers many attractive and efficient features compared to traditional two-arm trials, including fewer required patients, shorter time to treatment evaluation, and greater power to identify effective therapies.”10

The scope of the five reviews depended on the extent to which the available literature directly addressed adaptive platform trials. The review of consent and public engagement processes, in particular, drew on parallels with other “alternative” trial designs (such as cluster randomized controlled trials), given the paucity of published literature. The review of ethical considerations arising in connection with technical aspects of adaptive design included experiences in the use of these methods both in and outside platform studies.

The discussions at the meeting focused on platform trials with adaptive features, i.e., large multi-site studies governed by a master protocol, with multiple arms and with scope to remove or add arms and to adjust allocation criteria to the various arms in response to ongoing data analysis.

3. Key themes

A number of strong common themes related to the ethics and governance of adaptive clinical trials emerged in the discussions on the five reviews.

Challenging the myths about delays and timescales

Despite the widely held view that ethics review holds up clinical trials, the rapid reviews showed that ethics review is not usually a barrier to setting up and completing this kind of complex trial in a short time without sacrificing standards. Some COVID-19 adaptive platform trials began very rapidly because the relevant processes (including both ethical and regulatory review and contracting arrangements at individual sites) were all streamlined and prioritized. Other important factors identified by contributors included political and financial support, such as the active support of the Chief Medical Officers in the United Kingdom for a research-led approach to the pandemic through widespread recruitment to the RECOVERY trial and Government underwriting of manufacturing costs, so that studies of new interventions could be scaled up much more rapidly than usual.

It was noted that the highly practical aspects of “lean” project management – cutting out the “dead space” in standard study timetables – are ethically significant, as they can contribute to social value by identifying effective interventions more quickly. They also raise ethical questions with regard to what is not prioritized. When a limited number of research questions and studies have priority for funding, public attention and political support, it is likely to be at the expense of competing priorities. This highlights the importance of a public health perspective – one that takes account of all population health needs in setting research priorities.

Importance of pre-pandemic preparedness

Pre-pandemic preparedness plays an important role in achieving streamlined processes. Elements of the infrastructure necessary for such preparedness identified in the reviews include established networks, master protocols, simplified trial delivery to minimize the impact on already busy health services and plans for digital data collection (ideally integrated with routine data collection). A further key element, particularly in multi-country trials, is development of trusted relationships between research teams before the emergency. It was noted that such “soft capital” or “social capital” cannot be created overnight. Further thought should be given to the processes that enable such capital to be developed and maintained. “Sleeping protocols” (agreed protocols on standby, ready to be activated), although valuable, are not enough: actual activity is necessary to maintain those relationships and networks and to provide a base from which rapid scaling-up is possible during an emergency.

11 See, for example, the work of the PREPARE network in Europe: https://www.prepare-europe.eu/why-PREPARE1.html.

Social value and inclusion

The social value of adaptive platform trials during public health emergencies lies in their ability to provide evidence rapidly on which interventions are, and are not, effective in responding to novel health threats – hence minimizing the impact of the threat on populations and individuals. If this social value is to accrue to all – and not be restricted to privileged populations – the important question arises of who is to be included in study populations and hence represented in the resulting data. If groups traditionally considered to be “vulnerable”, such as children, pregnant women and minoritized populations, are inadequately represented, they will not benefit from the results of the research. Similarly, if research is conducted in only a few countries or regions, populations in other parts of the world may be less likely to benefit from the results.

This brings up the question of which interventions to select for adaptive platform trials, how the decisions are made and whose voices are included (see also below, under Governance). As not all interventions will be available or feasible in all settings, the choice of interventions to be included in a multi-country platform trial has ethical implications for future access. It was noted, for example, that adaptive platform approaches were used primarily for therapeutics and vaccine research during COVID-19 and not for non-pharmaceutical interventions. Moreover, research findings must be promptly translated into practice (including a commitment to and practical aspects of post-trial access) if the social value of research is to be realised. This will not be possible if study interventions cannot feasibly be scaled up beyond research sites in some countries.

Equity and sustainability in partnerships

To date, adaptive platform methods have been used primarily in the global north, although this is gradually shifting, the WHO-led Solidarity trial being a notable exception. It was noted that the dominance of global north leadership contributes to a risk that adaptive approaches may default to global north priorities without recognition of how this may influence the generalizability of the results and accessibility in the global south. Questions of equitable partnerships – promoted at institutional level through initiatives such as the Research Fairness Initiative – are important to consider in adaptive platform trials, including with respect to the manner in which studies are conducted at different sites, the roles and influence of the various partners and in terms of how the focus of research is decided.

It was highlighted that these considerations are important not only for the conduct and outcomes of individual platform trial partnerships but also for the future sustainability of research in particular settings or countries. How such major trials are conducted during emergencies is likely to affect future confidence in research, positively or negatively. Research practices that are not sensitive and locally acceptable may undermine the basis of any future research, however potentially valuable. The increasing emphasis on large-scale adaptive platform trials, involving large numbers of sites, participants and funding, might support consistent long-term investment in infrastructure in research in lower-income settings. If this is the case, questions of equity will become even more important and must be built into long-term research capacity and infrastructure support from the beginning.

13 The RECOVERY trial, for example, which started in the United Kingdom very early in the pandemic, is now partnering with hospitals in Indonesia, Nepal and Viet Nam (see https://www.recoverytrial.net/international).


15 https://rfi.cohred.org/
Governance

Adaptive platform trials raise novel questions for internal governance mechanisms. Most guidance in this area has been developed for single-sponsor, single-product studies. This is particularly challenging under the time pressure of a public health emergency (see Challenging the myths and Importance of pre-pandemic preparedness above). Questions raised during the discussion of governance included:

- How can values, such as the concerns about equity discussed above, be built into governance mechanisms?
- What is the place of governance arrangements in each platform trial? In particular, how are mechanisms for accountability balanced between the “centre” and individual sites or countries? How transparent are those arrangements, and who is responsible for deciding them?
- Who determines what goes into key documents such as partnership agreements, the terms of reference of the various parts of the governance system or material transfer agreements? And what scope is there for new partners to exercise any influence, as new sites are added to a trial that is already well established?

Other key governance issues included:

- The importance of both clarity and transparency regarding data and samples, including oversight arrangements, especially given the diverse regulatory approaches of different jurisdictions on how personal data may be used for research purposes.
- Compliance with key documentation, such as partnership agreements or material transfer agreements: what kind of monitoring is or should be in place, and by whom? How might governance include monitoring and reporting requirements?
- Scope for ethics expertise to be built into the broader governance structure of a trial – for example through an “ethics working group” supporting the trial or ethics expertise within a data safety and monitoring board. Such approaches (drawing on the experience of pragmatic trial networks) could enable ethical considerations to be raised and discussed during the ordinary business of the trial, in addition to the existing protection of ethics and regulatory review.16

Tension between universality and pluralism in platform trials

Platform trials are based on “master” protocols, and hence a degree of consistency is required among sites in order to produce meaningful results. The tension between such universality and the ethical imperative of conducting research in ways that are sensitive to the local context emerged as a cross-cutting theme throughout the meeting. It was noted that, while consistency with respect to the core aspects of the protocol will always be essential, there is scope for sensitivity and adaptation of other aspects of study conduct. These include appropriately designed recruitment and consent procedures for different sites and some discretion about which study arms are conducted at which sites. Other important factors affecting local acceptability include the extent to which the arms of the study respond to local needs and the role played by local stakeholders in governance arrangements (see above under Social value and inclusion and Governance).

16 See, for example the work of the NIH Pragmatic Trials Collaboratory: https://rethinkingclinicaltrials.org/.
Engagement

Meaningful engagement (variously described as community, public or stakeholder engagement, patient and public involvement, good participatory practices, consultation or dialogue) also emerged as an important cross-cutting theme. The specific feature of platform trials – use of a single master protocol at multiple sites and countries – raises the importance of effective engagement practices at the initial trial design stage, to ensure that the design is informed by as wide a range of perspectives as possible. The importance of transparency about the degree of influence of community stakeholders that is genuinely possible at different stages and under prevailing time pressures was emphasized. As noted above, there should be some scope to adapt the features of study conduct to make them locally appropriate and sensitive, although, in seeking such input, it is important not to appear to promise communities what cannot be delivered.

Most existing guidance on engagement, including WHO’s Good Participatory Practice toolkit, was developed for single research projects, with a beginning, a middle and an end. Platform trials, which are based on the development of networks and creation of long-term platforms across multiple countries, bring new challenges. This raises questions of how to achieve genuinely respectful engagement, allowing for a voice in both the choice of priorities for the platform trial and the way in which the research will be conducted. A further important role for guidance in this field could be to reinforce the importance of feedback to community stakeholders on the impact of their input. It was suggested that researchers are not usually opposed to doing this but may often overlook or underestimate the extent to which feedback is appreciated and valued.

It was also noted that there are few documented accounts of involving community stakeholders in the design and acceptability of COVID platform trials; however, this does not mean that such consultation did not take place. Anecdotally it did, albeit after a slow start at the beginning of the pandemic and primarily at the implementation stage. Members of the REMAP-CAP and RECOVERY teams, for example, described early on-line meetings with established public and patient involvement (PPI) groups to receive input for communications materials, informed consent forms and other public materials. For the Solidarity and REMAP-CAP trials, the urgency of developing and implementing trial protocols and the need for standardized procedures at all sites is likely to have limited opportunities for patient and public input into trial design and acceptability. For the RAPID trial (which used adaptive but not platform design), social restrictions and lack of funding were reported as barriers to early engagement.

Informed consent and public awareness

The complexity of adaptive platform trials (with respect to both the adaptive methods used and the number of arms) raises specific challenges for informed consent processes, in particular how best to share information about the features of the trial in ways that help people to make decisions. Issues raised by meeting participants included:

• Lack of empirical evidence about what people actually want to know or would find helpful in making a decision. Are people primarily concerned about risks? Should the possibility of addition of new arms or discontinuation of others during the trial be explained? Should participants then be alerted

if a particular arm is discontinued or a new arm added at some time during the study? More broadly, to what extent and how can the uncertainties of emerging and developing knowledge be recognized in consent processes?

- The role of “preventive” information as part of informed consent processes to forestall the impact of misinformation – particularly in the context of strong “anti-vax” sentiment and social media misinformation campaigns.

- The value of conducting research on these issues before any future emergency and finding ways of explaining key concepts in accessible ways (for example, talking about “tossing a weighted coin” to explain some randomization processes). Although there are many examples of imaginative ways of sharing information, little evidence is available on how effective they are.

It was noted that, in considering the specific informational challenges of explaining adaptive platform trials, it should be kept in mind that the information shared during informed consent processes is only one of the many factors that affect people’s decisions. People give or withhold consent for a wide variety of reasons, such as trust in science, trust in the person seeking consent or perceptions of possible personal benefit, including in response to fear of death.20

**Challenges of therapeutic misconception**

Government support for research-led emergency response can be important in enabling studies to be set up rapidly (see above under **Challenging the myths**). This could, however, add to therapeutic misconception if ministries of health are also promoting the introduction of authorized interventions, especially when the interventions included in the study are already licensed for other conditions. This is of particular concern when the motives for research participation are related to lack of access to treatment or fear.

**Technical aspects of adaptive design**

A number of features of adaptive trial design give rise to particular ethical challenges. It was noted that, in some cases, these are further complicated because they touch on issues for which there is currently no ethical consensus on what constitutes acceptable or best practice. These include:

- **Equipoise**: There is currently no clear consensus on how “equipoise” should be interpreted and when it should be considered to be disturbed (with the consequence that a trial should be stopped). Adaptive trials pose further challenges to this ongoing debate, because, by their nature, they draw on the data produced throughout the trial, in contrast to traditional trial designs in which there is a deliberate choice not to review the data early (except for monitoring safety).

- **Fair treatment of participants**: An inherent injustice in adaptive trial methods is that participants recruited later in the trial are more likely to be assigned to a more effective intervention (with the caveat that what works well in one setting may not necessarily work well in another). There is also a wider collective benefit in adaptive trial methods in that fewer participants will be required in order to obtain a meaningful result, thus reducing the risks of harm overall. (See above under **Consent** for a discussion of what potential participants might need to know to provide informed consent.)

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• **Access to effective interventions for study participants**: Entitlement for participants to be unblinded and given access to a trial intervention that is shown to be effective (i.e., when they did not receive the beneficial intervention) is more complicated in multi-arm adaptive trials, such as when a placebo or usual-care arm is still required for other arms of the study.

• **Availability of products in head-to-head studies**: It was noted that some developers and sponsors are unwilling to make their products available for head-to-head comparisons with other products. This creates significant problems for ethical study design, particularly when interventions offering some benefit are already licensed and hence placebo-controlled trials are very difficult to justify.

**Research capacity strengthening and knowledge transfer**

Adaptive platform trials draw additional attention to the importance of capacity strengthening and effective knowledge transfer between research stakeholders.

• **For ethics committees**: The complexities of adaptive trial methods require that ethics committee members have both sufficient knowledge and sufficient confidence to review study proposals. It was noted that the ability of researchers to explain their proposals plays an important role in effective review. The complexities of reviewing adaptive trial proposals add to the existing pressures on ethics review infrastructure in many countries, including with respect to funding and the capacity of their systems, their staff and their members. During public health emergencies, capacity constraints are likely to be exacerbated: members, in particular, experience many other pressures and commitments as part of emergency response, and the increase in the volume of research proposals in response to an emergency is rarely accompanied by additional funding for ethics committees.

• **Within networks**: Issues of capacity strengthening and two-way knowledge transfer also arise in platform trial networks with respect to the need for investment in sustainable infrastructure for partners working in lower-income settings: from supporting the development of specialist skills such as the statistical expertise required to enable data to be processed at study sites, to much broader elements of infrastructure, including library access and career pathways for academics, and national regulatory structures.

**Value of dialogue**

The value of dialogue emerged as a significant common theme during the discussion. This includes dialogue:

• within and between different parts of the system (for example between regulatory and ethics review systems) to avoid duplication and delay;

• between researchers and ethics committees, to improve understanding and minimize delays; and

• between ethics committees, for better-informed and -coordinated decision-making and to avoid duplication (while the decision-making authority remains with individual committees).
4. Remaining evidence gaps

One of the aims of the meeting was to identify remaining evidence gaps – both those that could potentially be filled from the existing evidence base with additional analysis and those that would require new data collection. A full list of all the research questions proposed during the meeting is given in Annex 3. The broad areas were:

- learning from the major COVID-19 platform trials what worked well and could be translated to other areas of research or other contexts;
- identifying what is required to maintain sustainable networks between emergencies;
- understanding the experience of researchers in the global south involved in COVID-19 platform trials and mapping processes to promote more equitable partnerships and to support global south leadership;
- mapping the engagement that took place for the COVID-19 platform trials, much of which is currently undocumented;
- understanding the challenges and experiences of ethics committees in reviewing platform trials and how they could be best supported;
- understanding the relations between ethics review and other kinds of oversight and how they could best be managed in complex trials, especially in emergencies;
- analysing delays from the perspective of researchers: where the barriers were and how they could be reduced;
- understanding what potential participants would like to know about adaptive platform trials in order to decide whether or not to take part; and
- learning more about uptake, exploring what led to prompt uptake of effective interventions and how equitable access was.
5. Scope for further guidance

A number of areas were identified in which additional guidance is likely to be welcomed by research stakeholders, whether as part of new guidance on the ethical oversight of adaptive platform trials or in other formats (for example through developments in existing guidance such as Good Participatory Practice). These include:

- specific discussion of and guidance on the particular ethical issues raised by the design features of adaptive platform trials, such as the complexity of equipoise (for example, following the model of WHO’s guidance on human challenge trials);
- guidance on what information is necessary in informed consent documentation for participation in adaptive platform trials, accompanied by examples of good practice in explaining key features in different regions and contexts; and
- specific guidance on engagement for adaptive clinical trials.

A further important consideration is whether such guidance should be specific to use of adaptive platform methods during emergencies or be more generally applicable.

It was suggested that, in addition to drawing on the five reviews and the outcomes of the project meeting, a helpful step in developing such guidance would be to convene a meeting of some of the research teams working on major adaptive platform trials to explore further their experiences and insights.
Annex 1. Participants

Project leads and authors

- Joseph Ali, Johns Hopkins Berman Institute of Bioethics, Baltimore (MD), USA
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- Katherine Littler, Health Ethics and Governance unit, WHO headquarters
- Lee-Anne Pascoe, consultant, Health Ethics and Governance unit, WHO headquarters
- Andreas Reis, Health Ethics and Governance unit, WHO headquarters
- Katharine Wright (rapporteur), United Kingdom
Annex 2. Five commissioned literature and evidence reviews

Relation between adaptive platform trials and policy-making

- Is there a clear relation between the social value of conducting trials and uptake into policy-making, especially in an emergency context?
- Are there particular issues in adaptive trial designs that should be considered – e.g., not the “gold standard”, weight of evidence?
- Are there models of good practice? From past outbreaks, from COVID-19, more generally?
- What are the potential conflicts to be avoided?

The ethics of adaptive clinical trial design

- What are the ethical implications of adaptive clinical trial features such as frequent interim analyses and response adaptive randomization?
- How do adaptive trial design features affect the notion of equipoise?
- How do evolving standards of care and increasing access to newly authorized, efficacious interventions in public health emergencies affect the conduct of adaptive trials?
- How should trial unblinding be done in the context of newly authorized interventions?
- How should trialists counter potential therapeutic and preventive misconceptions on the part of study participants?

Engagement models and needs

- Given the scientific and statistical complexity of these trial designs, what work has been done to find appropriate consent models – e.g., for understanding issues of randomization, acceptance of the model of randomization?
- What type of guidance is there on community engagement for these trials? How has it evolved, both during and before COVID?
- What are the current models and practices of community engagement?
- What type of empirical work has been done on appropriate engagement practices?
The importance of fair, inclusive research practice for adaptive trial designs: types of collaborations that have emerged and are necessary

- How are multi-site, multi-country studies being set up?
- Who are the decision-makers? Who should be included in making decisions and at what stage?
- How do they allow for differences in cultural contexts in the study design?
- Are alternative oversight structures being explored?

Oversight and governance of these trials during COVID-19

- What is the current guidance on these trials?
- How are they reviewed and governed in practice – by, e.g., research ethics committees, data and safety monitoring boards?
- How are they reviewed at local, national, regional and global levels? What is the relation among the different oversight mechanisms (including oversight structures within the trial, such as a data and safety monitoring board)?
- What main issues are emerging during review?
- What is working and what is not? Why?
- Are new models being explored, e.g., AVAREF mutual recognition models, sub-committees with specialist expertise?
- Is new guidance necessary? If so, what type of guidance? Is it necessary for adaptive trial design or clinical trials more generally? Should there be an emphasis on specific needs or contexts?
Annex 3. Suggested areas of future empirical research

- Improving project management for clinical trials in public health emergencies: mapping the steps that need to be taken, from formulation of the study questions to regulatory approval and access, in order to determine how the process can be made as “lean” as possible; exploring differences between centres, countries and jurisdictions; and identifying how good processes could be built on. One approach would be to draw on existing work by PREPARE to avoid duplication and then consult the principal investigators of major trials.

- Understanding how networks develop and how partners are chosen: could include consulting with Solidarity, RECOVERY and other trials on their experiences of working with global south partners.

- Understanding how best to maintain networks sustainably between emergencies and hence ensure a rapid response from the start of an emergency.

- Exploring how what worked in investigational trials could be used in other kinds of research – particularly in the use of non-pharmaceutical interventions.

- Prospectively, mapping processes for identifying and promoting equity-enhancing systems. What information is necessary to evaluate the ethical quality of partnerships, and what trade-offs are acceptable – both empirically and ethically?

- What can be learnt about global south leadership in global partnerships from other areas of research, e.g., from initiatives such as H3 Africa and the Research Fairness Initiative?

- Further empirical research on experiences of public engagement during COVID-19: Very little is reported, but, anecdotally, it did take place, albeit after a slow start at the beginning of the pandemic. Capturing that experience – what happened, how it was perceived by the wider public and how it affected the conduct of specific platform trials – could be valuable for the future.

- Understanding consent: empirical investigation of consent processes in the COVID-19 adaptive platform trials (i.e., not just informed consent documentation, but also other elements of the process of seeking consent) to understand how people made decisions about taking part in adaptive trials, what informed their informed consent (or refusal), and what information they would ideally have liked to have. Some of this could be done by follow-up in pandemic trials, i.e., linking with existing data points.

- Identifying whether consent processes provide scope for future follow-up – whether in the form of permission for re-contact, consent for secondary use of data to answer related research questions or broad consent.

- Recruitment from the perspective of researchers: including whether any special effort was made in the COVID-19 adaptive platform trials to reach specific under-represented groups (anecdotally, this happened, e.g., when it became clear that certain minoritized groups were not being included; however, this is not well documented).

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• Identifying **who was actually recruited** during the COVID-19 adaptive platform trials: for example, the extent to which children, pregnant women and other groups traditionally regarded as vulnerable were included. Whose data is in the dataset and whose has been excluded? And to what extent might that be because of the particular model of adaptive platform trial as opposed to other reasons such as lack of research infrastructure in some settings?

• **Understanding delays from the perspective of researchers**: the relative roles of factors such as contracting issues, relation between regulatory and ethics review, delays in one particular committee or a long back and forth between different stakeholders, complications of version control when a number of committees are reviewing the same protocol, etc.

• **Challenges and experiences of research ethics committees**: identifying what information about adaptive trials reviewers require, common problems in proposals, key training and capacity support needs and relations with other parts of the oversight and regulatory system.

• **What actually informed how research ethics committees in different countries reviewed the COVID-19 platform trials**: understanding the role of factors such as the confidence of committee members in this kind of trial design, the resources and infrastructure for committees and their members, scope for parallel and joint reviews and political attitudes. This could provide a basis for future policy to support committees.

• **Uptake**: understanding the extent to which the findings of the adaptive trials have changed practice, what was required to achieve that and whether the uptake was different from that achieved from other kinds of trial. This could include analysis of the cost savings achieved by no longer offering treatments that have been demonstrated to be ineffective. Various contexts should be considered, including what responsibilities arise for whom, especially when repurposed interventions in a study are not available or affordable in some settings.