Global Forum on Bioethics in Research

Meeting report:

Ethics of alternative clinical trial designs and methods in LMIC research

Bangkok, Thailand

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Executive Summary

Ground and justification: The Global Forum on Bioethics in Research convened in Bangkok, Thailand in November 2017, to explore the "Ethics of alternative clinical trial design and methods in low- and middle-income countries (LMICs) research". With experts in bioethics, clinical trials, statistics, epidemiology, public policy and clinical research from 35 countries, the meeting used case study presentations and first hand experiences as the basis for discussion. With a focus on cluster randomised trials (CRTs), stepped wedge CRTs (SW-CRTs), adaptive platforms and controlled human infection models (CHIMs) the meeting explored when the use of these designs is justified and what ethical challenges they present.

- **Alternative clinical trial designs and methods can offer a number of potential advantages over the conventional individually randomised clinical trial, including accelerating vaccine or drug development and making the clinical trial process more socially acceptable**. They enrich a researcher's armoury, allowing them to choose from a broader range of designs and methods and to adopt the most scientifically suitable, efficient, ethical and context appropriate. However, **these designs are largely unfamiliar and it became clear at this meeting that there is still a long way to go until researchers in LMICs can effectively utilise them.**

- Novel designs and methods should not be labelled 'alternative' as may suggests they are somehow flawed in comparison to the traditional individually randomized control trials (RCTs). Instead of talking about 'alternative' study designs, it's more helpful to ask: **what is the *best* design for the goals and context of this study**? Being explicit about the goals and context will help a researcher identify the best design based on the specific research question and the context in which the study is going to take place. **It is not that one type of design or method is in general better or 'more ethical' than others.**

- Being explicit about goals also helps clarify some of the ethical and regulatory questions about the study. However, there are **grey areas** (particularly in the use of stepped wedge studies) between evaluating roll-out of a new intervention, and conducting research into how the intervention works. In such grey areas, it is helpful to separate out what may be required in terms of regulation (for example, if the law requires scrutiny by a Research Ethics Committees (REC)); and what is actually ethically demanded (what kind of oversight would help identify and respond to ethical concerns). There is a need for some kind of mechanism (not necessarily replicating REC review) that would exercise **appropriate ethical oversight of studies that are primarily concerned with evaluation and quality improvement** and that fall outside traditional definitions of research. In this context, it is important to ensure that a clear justification is provided for the approach taken (i.e. finding and justifying appropriate ethics input).

- Many of the ethical issues that arise in these study designs are common to other kinds of research. For example, achieving valid consent; reimbursement and compensation that is fair but does not constitute undue inducement and post-trial access to treatments/interventions. Issues that may complicate these 'standard' concerns include determining **who is actually a study participant in a CRT and questions of public acceptability and impact on trust, particularly in controlled human infection studies**.

- Community engagement can contribute to building trust in research and is vital for addressing the beliefs or cultural norms that may impact on public acceptability of novel designs and methods. **Engagement activities should be underpinned by empirical data on what is acceptable and important to local communities and regulators, including preferences for how information is provided.** For example, it would be important to obtain empirical data on whether or not particular trial designs (e.g. CRTs where clusters of participates are given the same intervention) are more acceptable in practice to local communities and potential participants. This seems intuitively likely but there is no firm evidence.

- For research to have the greatest impact, governments and policy makers must have confidence in the validity of the results and be willing to act on the findings. Otherwise, this calls into question the social value in conducting trials if there will be no impact. **Researchers and sponsors should involve government and other stakeholders in *advance* for trials that are meant to impact policy or public health system operations, and the appropriate level(s) of government should be engaged (sub-national, district, etc.).** This engagement should address both implementation and sustainability and continue throughout the research process. This is especially important in contexts where non-traditional designs are unfamiliar to regulators and policy makers, and where the resulting evidence may be seen as inferior to evidence from a traditional RCT.

- There is limited international guidance on these trial designs and scarce guidance specific to LMICs. There was no clear consensus at this meeting on the need for new ethical guidance for these designs – or for LMIC-specific guidance. But there was consensus on the need to build capacity locally to propose, review and regulate these designs and methods. **Training researchers, RECs and regulators in the science of these trials (e.g. in the statistical calculations to determine sample sizes and the algorithms and mathematical models required to implement the designs) should help avoid a 'precautionary' approach, whereby RECs and regulators reject any kind of novel design or method**. International organisations such as the World Health Organisation or the Pan American Health Organisation can take the lead developing these capacities. Research grants could also usefully include additional provision for training/support for RECs, particularly in low income environments.

Introduction

The Global Forum on Bioethics in Research (GFBR) convened in Bangkok, Thailand in November 2017, to explore the *"Ethics of alternative clinical trial designs and methods in low- and middle- income country research"*. With experts in bioethics, trial design, biostatistics and research from 35 countries (see map of GFBR participants' countries), the meeting delved into ethical issues with respect to the use of these trials and methods.

The meeting topic was chosen because of the increasing use of alternative clinical trial designs and methods in place of the conventional randomised controlled clinical trial (RCT) in LMICs. These approaches – including adaptive, cluster randomised and stepped wedge designs and controlled human infection models – offer several potential advantages, including accelerating vaccine or drug development and making the clinical trial process more socially acceptable. However, the ethical implications of these designs on risks and potential benefits to participants, consent, scientific rigour, trial efficiency (including study population size), have not been adequately addressed. These uncertainties are further compounded by current guidance which was largely written without special consideration of new trial designs, leaving researchers, research ethics committees and regulators with little support in how to evaluate, implement and run these often complex trials.

This GFBR meeting addressed the need for the global bioethics and research community and regulators to come together and discuss when the use of an alternative design or method is justified and whether any morally relevant differences exist between the conduct of alternative designs and methods in LMICs in comparison to high income countries (HICs). The meeting built on the important discussions that took place at GFBR 2015 concerning the use of adaptive trial designs in emergency epidemic situations.[1] By providing a mutual ground for discussion and a shared understanding of the challenges and opportunities presented by alternative approaches, the GFBR aims to promote the appropriate and ethical use of these trials and methods. Through such use their full potential to address the health needs in LMICs can be realised.

[1] GFBR 2015 'Emerging epidemic infections and experimental medical treatments', Annecy, France http://www.gfbr.global/past-meetings/10th-forum-annecy-france-3-4-november-2015/

Figure 1 GFBR participants: 93 participants from 35 countries came together to discuss this important issue with a wide range of academic and clinical expertise: bioethicists, clinicians, statisticians, community practitioners, policymakers, social scientists, regulators, and funders, at all levels career stages. 58 participants were from LMICs.

1. Choosing the best design or method for the research question

GFBR participants agreed that we should move away from talking about 'alternative' designs as this suggest they are somehow flawed in comparison to the traditional individually randomized control trial (RCT). Instead we should ask **what is the best design for the goals of the study**. It is not about one design being generally better than others but about finding the right design for the research question.

There are a variety of reasons to use a non-traditional design including:

- **Scientific**: validity, efficiency, when the research question relates to effectiveness, as opposed to efficacy and when the goal is to measure and/or affect change at the community or population level where the outcome expected is population based change
- **Practical**: recruitment, consent, feasibility in implementation, costs, cultural or social preferences
- **Ethical:** risk mininisation and maximization of benefits

Having a contextual understanding of the research and its long term objectives is key to determining when these designs are ethically and/or scientifically preferable. The context will depend on the:

- **Nature of the health or disease condition being studied**: public/population health, emergency
- **Nature of the intervention**: likely effectiveness, available range of therapeutic options, duration in evaluating study endpoints, risk vs benefits
- **Resources**: availability of the intervention and personnel
- **Preference of stakeholders**: e.g. community acceptability
- **Behaviour of participants**: e.g. sharing of medicine

The case studies presented during the course of the meeting demonstrated some of the reasons why a certain design might be employed (see individual sections below).

Ethical issues

Many of the ethical issues that arise in these study designs are common to other kinds of research e.g. achieving valid consent; reimbursement and compensation that is fair but does not constitute undue inducement; post trial access to treatments. Ethical issues that may complicate these standard concerns include:

- **Methodological** (scientific rigour, applicability of the concept of clinical equipoise, equity issues in relation to delaying roll-out of an intervention and standard of care for non-intervention groups)
- **Distinguishing between research and implementation** (for SW-CRTs)
- **Determining who is a study participant in a CRT** (with implications for consent and post-trial provision obligations)
- **Informed consent** (complexity of information, reasons for a waiver, role of gatekeepers)
- **Public acceptability and impact on trust** (particularly in CHIMs)
- **Political interference** (e.g. choice of first cluster versus randomisation in SW-CRT).

2. Cluster randomised trial

Cluster randomised trials (CRTs) are commonly used in knowledge translation, public health and health services research. They are experiments in which groups of individuals — rather than independent individuals — are randomly allocated to interventions while the outcomes are measured on individuals. Common clusters in health research include medical practices, hospitals, nursing homes, neighbourhoods and communities.

The intervention may be delivered to:

- the cluster as a unit (cluster-cluster trial)
- health professionals (professional-cluster trial)
- individual cluster members (individual-cluster trials)

The timings of the intervention may be:

- parallel cluster trials: where the intervention and control clusters take place at same time
- stepped wedge studies: where there is roll-out of an intervention – all the clusters start at the control condition, and the intervention is then rolled out to all clusters in random order (see section 3)

Participants in **case study 1** provided individual consent and so in principle a traditional RCT could have been chosen. However, the research was performed in a culture of close familial relationships where medicines are commonly shared. The researchers chose cluster level randomisation to reduce potential contamination and to promote the scientific validity of the results.

Case study 1: Ethical issues of the PolyIran study: A cluster randomized trial nested within Golestan cohort study

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This CRT aimed to assess the effectiveness and safety of polypill tablet for primary and secondary prevention of cardiovascular diseases. The justification for using cluster randomization was based on the close familial relationships in the population being studied and the common behaviour to share medicines. Cluster randomisation at the level of villages was chosen to minimise the risk of contamination through pill sharing. The researchers faced challenges in obtaining informed consent and determining a fair policy for post-trial provision of the Polypill.

Cluster selection: Study designs should be appropriate to the research question so data are reliable and interpretable. For example, an individually randomized trial would be impracticable and uninterpretable for an intervention at a population level (e.g. such as a treatment in a hospital). A CRT would be more appropriate providing fidelity is ensured through sufficient cluster sizes; insufficient sizes result in too much 'noise' making it hard to discern the impact of the intervention. Fidelity across the clusters may be easier to ensure for a drug intervention but is more difficult to ensure for a lifestyle/behaviour interventions.

Case study 2 demonstrated the issues of defining clusters to both minimise contamination and maximise fairness in a community. Pregnant women accessing antenatal care in urban Malawi were recruited into either the Standard of Care (SoC) arm (involving an invitation letter to their male partner offering HIV testing) or one of five intervention arms offering their partners oral HIV self-test kits. Three of the five intervention arms additionally offered the male partner a financial incentive. Male partners were randomised based on the day of the week that their female partner attended an ante natal clinic. This approach gave rise to difficulties when men on different intervention arms later came to the clinic, on the same day, to see the HIV counsellor. The men shared information about the study leading to confusion for those in the non-incentive arm as to what they were supposed to receive at the end of the clinic attendance. GFBR participants agreed that defining each clinic as a cluster would have prevented this confusion and resulted in everyone at the same clinic being treated fairly and equally.

Case study 2: Lessons from an adaptive multi-arm multi-stage trial of strategies for improving linkage into HIV care or prevention in Malawi

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The partner-provided self-testing and linkage (PASTAL) cluster randomized trial was a Phase II adaptive multi- arm multi-stage cluster randomised trial allocating antenatal care (ANC) clinic days to six different trial arms. An ANC day was the cluster. Pregnant women accessing ANC in urban Malawi for the first time were recruited into either the standard of care arm (invitation letter to the male partner offering HIV testing) or one of five intervention arms offering oral HIV self-test kits. Three of the five intervention arms additionally offered the male partner a financial incentive (fixed or lottery amount). The researcher came across ethical challenges with regards to the choice of a cluster, informed consent, potential lack of equipoise, and post-trial access to interventions.

Consent: GFBR participants acknowledged the ethical challenges of informed consent for people in vulnerable situations. This may involve high levels of illiteracy, difficulties in retaining information provided verbally in a one-off situation and where their capacity to withdraw consent at a later stage may be compromised. **Case study 1** dealt with these issues when obtaining individual consent in a community with high levels of illiteracy. Local interviewers were trained to provide information in a comprehensible manner about the intervention that was administered at an individual level, while the trial was at the cluster level. However, these concerns are general issues for any research with illiterate and vulnerable populations.

Waiver of consent: GFBR participants considered that a waiver of consent is acceptable in certain circumstances, for example:

- **in cluster-cluster trials when it is impracticable to obtain consent,**
- **where an intervention is a minor change to a standard procedure and**
- **where risk to participants is minimal.**

Parallels were drawn with implementation of public health policy where consent is not sought on an individual basis. Similarly, for registry based studies data are collected but participants don't give consent as being part of the health system implies consent.

The risks of participation should feed into the decision on whether a waiver is appropriate. For example, **Case study 1** looked at safety and efficacy outcomes in which a waiver would be hard to justify. On the contrary, HIV testing in **case study 2** is something that a person might be exposed to outside the study and so a waiver is arguably more appropriate.

In some cases, where consent has been waived, it may be important to sensitise or seek authorisation from the community. For example, consultation could take place with gatekeepers about what matters to the community or there could be broader information sharing.

Incentives and coercion: **Case study 2** involved the provision of a financial incentive to self-test for HIV. Some GFBR participants considered this coercive but others thought it would be unethical to use people's time without providing financial compensation. It was considered important to distinguish between compensation, incentivisation and an incentive as the intervention. 'Coercion' was considered an unhelpful term in the context of **case study 2**; the intervention was provided in a good healthcare infrastructure and could lead to beneficial treatment.

Community acceptability: GFBR participants considered that small communities may be more accepting if they are all given the same intervention as they will not feel individually discriminated against. They may also be more likely to agree to participate in the trial if they receive the same treatment as their peers. Some GFBR participants considered that it might therefore be easier to explain and get community level approval for CRTs. In particular, the community may be more willing to participate if there is an assumption that the intervention is more effective than the SoC.

Anecdotal examples were given at the meeting: In the Gambia, studies that expose the whole community to the same intervention work better. Also, early involvement of religious or community leaders promoted community acceptability and motivated others to participate. Similarly, in parts of Thailand, community leaders' endorsement has been very important in getting community buy-in for research. In China, different communities respond very differently – some will decide on an individualist basis, while others are strongly influenced as a cultural group. But this could be more an argument for community engagement than for cluster design per se. It was acknowledged that some cluster trials still have differentials between communities – e.g. stepped wedge where some clusters will get later access than others.

GFBR participants agreed community engagement can contribute to building trust in research, which is vital for addressing the beliefs or cultural norms that may impact on public acceptability of novel designs and methods. **Engagement activities should be underpinned by empirical data on what is acceptable and important to local communities.** For example, empirical data is needed on whether or not cluster trials are more acceptable to individuals and their communities in different cultural contexts.

Obligations of researcher, sponsors and governments for post-trial access: The case studies shed light on the issue of post-trial access, a general issue in research ethics but arguably of greater pertinence for health policy and health services interventions. **Case study 1** was established on the premise that if the polypill was found to be safe and effective, all study subjects would receive the treatment after termination of the project. However, there were concerns about the feasibility of providing the polypill to subjects in the long term. There was also an issue of fairness: the usual care arm participants in the trial (who were part of the original cohort but were not selected for either of the polypill or minimal care arm) were not going to receive the polypill after termination of the project. **Case study 2** showed a financial incentive improved the primary outcome but policy makers were unwilling to scale up or pilot the intervention within their programs once the research had finished.

Both cases highlight the need for researchers - and sponsors - to involve government and other stakeholders in *advance* for trials that are meant to impact policy or public health system operations, and the appropriate level(s) of government should be engaged (sub-national, district, etc.). Engagement should address both implementation and sustainability. Otherwise, this calls into question the social value of conducting trials with these types of interventions if there will be no impact. GFBR participants agreed that researchers' plans should explicitly address post-trial access and include a commitment to advocate for up-take if the intervention is shown to be effective. Before generating evidence, researchers should talk to policy makers about the range of potential scenarios. It is important to start these conversations early and to communicate regularly during the research process.

It was noted, however, that guaranteed post-trial access can have unintended consequences. There were examples from countries where by law every intervention that proved effective must be given forever to the research participants. This resulted in a drop in chronic disease research. Different levels of guarantee could be required and this could become part of the risk/benefit analysis.

GFBR participants discussed the role of social science in ethical design of trials and how this might facilitate the engagement of all stakeholders from the beginning of the process - including policy makers. Examples were given from countries such as Canada where research translation and engagement with policy makers and stakeholders are now built into proposals for trials and are a crucial step in being awarded a grant. Policy makers are embedded in the process from the very beginning. An anecdotal example was given from Thailand, where vaccine trials used this model - despite it not being mandatory - and found it to be successful.

A broader question is whether policy-makers treat CRTs as gold standard evidence or if there is a need to elevate cluster trials to make sure they're treated as such and can have an impact on policy. For the research to be worthwhile, the government must accept the validity of the study. There may be a risk of selection bias in cluster trials (e.g. if community information sessions let people work out which arm they are in) but there can equally be risks of contamination in individual RCTs as described in **case study 1** where there was a culture of sharing medicines. There is no reason that a properly powered CRT is less effective than an individually randomised RCTs, but it was acknowledged that power calculations are difficult to do in clusters and there is a risk of being underpowered. Some GFBR participants considered this issue to be more acute in LMICs where the necessary expertise in biostatistics may be lacking.

Health record linkage and big data: GFBR participant envisaged the wider use of CRTs in future given the advent of electronic health records being used for research. Big data CRTs could be used to perform real-life evaluations of which treatments are better than the others or which hospital performs certain procedures more effectively than another hospital. The next 5 years will likely see an escalation in the use of CRTs in this context, raising questions about the ethics of using routine patient records for research.

3. Stepped wedged cluster randomised trial

A stepped wedge trial (SW) is a CRT cross over design in which clusters cross over in one direction only (from control to intervention). They are often used to evaluate an intervention that is destined to be rolled-out based on limited evidence. There are two forms of SW-CRT:

- **Cohort**: the same subjects within the clusters are being followed over time, hence the crossover between treatments is not only at the cluster level but also at the subject level.
- **Cross-sectional**: new subjects are being included after each step, which means that the crossover of treatments is only at the cluster level. Under this design not all participants will receive the intervention.

Case study 4 highlighted several reasons for choosing a SW-CRT design, including the fact that rolling out a large-scale public health intervention at one point in time was logistically unfeasible. Gradually rolling-out an intervention under a SW-CRT design allowed the researchers to learn during the process, and the implementation was refined at each step. It was also suggested that from a community viewpoint SW-CRT was likely to be more acceptable (than a standard CRT) as - in their study - everyone would receive the intervention by the end of the trial.

Case study 4: ATMIYATA: Testing effectiveness of counselling delivered by community volunteers to people with common mental health issues in rural parts of Gujarat, India: Step Wedged Cluster Randomized Trial (SWCRT)

Kaustubh Joag, Indian Law Society

ATMIYATA intervention involves a two-tier community led mental health model that develops capacity of community volunteers to identify and provide basic, low intensity counselling to persons with common mental disorders. The intervention employs use of films covering social issues like domestic violence leading to mental health issues to raise community awareness. A cross over unidirectional SW-CRT was employed as a better alternative to a conventional RCT from a logistic, social and political view point. The researchers found it challenging to specify a formal gatekeeper as per the definition in the Ottawa statement. They also faced challenges in relation to clinical equipoise and recognised the need to have a protocol for care principles in the control area. In addition, the cluster randomization process was influenced by health officials and a politician, who suggested a specified block in the district should be the first cluster.

Modifications and adaptations: SW-CRTs are frequently used to refine implementation during roll-out of an intervention. Some GFBR participants considered it due diligence to stagger implementation and make sure an intervention works once it is rolled out into a 'real-life' setting. Otherwise, resources could be wasted rolling out a policy that's been shown to work in one context but does not necessarily work in others. SW-CRTs are also often used when – due to economic, political, human resource reasons – the intervention will be rolled out gradually anyway. This presents an opportunity to learn about the best way to implement the new intervention (especially as new resources and modes of implementation might become available for the intervention over time).

GFBR participants recognised that policy makers may prefer SW-CRT designs as they help evaluate evidence and modify roll out before starting the next cluster and so answer for real-life adjustments – but does this modification change the research question? **Case study 4** took this staged approach, publishing the results of a pilot before receiving funding to scale up. The case presenter argued that modifications are important for implementation to be more productive (e.g. through training) but also because in real-life the research faces problems that may not have been anticipated at the outset. In this case RECs were notified of the modifications and the results were time adjusted. Confounding effects of the time of exposure with a SW-CRT can be a problem but this can be accounted for by adjusting the results for time (i.e. allowing for the possibility of changes over time which can affect the outcome, such as how a service was delivered). However, some participants noted that there have been articles in reputable journals where time adjustment didn't happen: this affects the status of SW-CRTs in the hierarchy of evidence.

The influence of dominant figures – such as politicians – was highlighted in **case study 4** where the first cluster was selected for administrative and political reasons. GFBR participants acknowledged that political interference cannot be ruled out and that the choice of first cluster can be influenced by other reasons too (e.g. logistical ease, greater need in a particular district etc.). This results in a 'quasi' randomised trial, which risks making the data less influential. However, it is possible to overcome the bias which comes from selecting districts which are preferred by policy makers or to discount these clusters from the analysis.

Equipoise: SW-CRT is used in situations "where an intervention under study has shown to be effective in controlled settings" [2] or where there is "a prior belief that the intervention will do more good than harm, rather than a prior belief of equipoise"[3]. Such starting assumptions call into question the ethics of delaying roll out of an intervention that is thought to be preferable to the standard intervention.

Many GFBR participants felt that a presumed evidence of superiority of an intervention raises issues of fairness; would it be ethical to withhold the intervention from some clusters in such cases? And on what grounds would such a delay be acceptable (e.g. logistical, administrative, political, research design/science)? The trade-offs (e.g. benefit to the individual vs benefits to society) should be considered and a transparent discussion should take place with the different stakeholders.

If equipoise is to be an effective concept it should be understood contextually. Foundationally, it is about uncertainty in the relevant domain of activity and will rely on many components (e.g. the public health provider, institutions, cultural issues etc.). So, while there is a broadly held intuition/belief that it's unethical to knowingly expose a participant to an intervention that is known to be inferior (e.g. the SoC) it may be necessary to contextualise the intervention before roll out as a real policy. For example, it may be that the intervention has proven to be efficacious, but there is limited knowledge on how it will work in practice and its effectiveness in a particular LMIC setting.

In general, the control group in a SW-CRT receive the SoC. Some GFBR participants argued that you are not doing harm to this group by withholding the potential benefits of the new intervention; this is different to withholding all forms of treatment. However, the SoC in some areas may be very low. Researchers could try and make each 'step' shorter to minimise the duration of the SoC or could incorporate a rescue function within the design so researchers can respond if there's a dire need. However, it is important to be realistic about the options genuinely available to those conducting the research. It should not be solely the responsibility of the researcher to ensure treatment provision or access, which is primarily an issue related to the broader context of the health care setting and prioritization. This makes it difficult and a hard balance to strike when assessing the responsibilities of researchers.

Who counts as a research participant? The issue of determining who exactly is the research participant (and who should provide consent) is common to both CRT and SW-CRT designs. **Case study 2** involved the recruitment of men through their pregnant partners and as such it was impossible to obtain written consent from the male partner despite them being the target population. A waiver of informed consent process was sought and granted by the institutional review boards.

Many GFBR participants were of a view that the male partners were participants and should have been consented; they received an intervention and were being impacted by the study. Arguably, the researchers themselves recognised the men were participants as they sought a waiver of consent. Although GFBR participants considered that consent should have been taken, the appropriate method was moot – some

[2] Mdege et al Systematic review of stepped wedge cluster randomized trials shows that design is particularly used to evaluate interventions during routine implementation. J Clin Epidemiol. 2011 Sep;64(9):936-48. doi: 10.1016/j.jclinepi.2010.12.003. Epub 2011 Mar 16.

[3] Brown and Lilford The stepped wedge trial design: a systematic review BMC Med Res Methodol. 2006; 6: 54. Published online 2006 Nov 8. doi: 10.1186/1471-2288-6-54

suggested verbal consent. It could be argued there was implied consent as the male partners had tested themselves and they had received an informational letter. However, they might not have known that they were being asked to self-test in the context of a clinical trial.

Health care professionals are also potentially participants in CRTs and SW-CRTs, though rarely identified as such. In **case study 3** health care providers and the traditional birth attendants were required to deliver an intervention and had no option to opt-out. Should they have been free to refuse the training and is their informed consent required?

Research ethics committees should use the following questions to help them determine who is the participant:

- **who is the focus of the services or intervention?**
- **whose behaviour is the research trying to change?**
- **from whom are we collecting private health information?**
- **what's the outcome and what is being measured?**
- **in turn, for each group of potential participants, what is the risk? Is there any risk to them that would not be the case if they were not involved in the research (including physical risk associated with an intervention and risk of disruption to social units)?**

These are complicated questions but they may help define what is ethically demanded in terms of consent.

Case study 3: 'Que Vivan Las Madres': Scaling up an integrated approach to reduce maternal and perinatal mortality in Northern Guatemala – A stepped-wedge cluster randomised trial (SW-CRT)

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"**¡Que Vivan las Madres!**" (QVLM) or "long-live mothers" aimed to determine if a package of interventions could increase the number of women giving birth in a health centre to help improve the delivery care of complicated deliveries, thereby decreasing the number of neonatal and maternal deaths and morbidity rates. The study gave rise to a range of ethical questions that are common to SW-CRT, namely: Was this study research; or should it be subsumed under the umbrella of service evaluation? Was it justifiable to delay the roll-out of the intervention that had promising effectiveness? Should the health care providers and the traditional birth attendants have been considered research participants? If so, what follows from this? What should each group have consented to and is the use a waiver of consent appropriate in this SW CRT?

Gatekeepers: The language of a 'gatekeeper' and their exact role was new to many GFBR participants but the idea of a community leader or someone who could provide an entry into the community and whose buy in was important was familiar to everyone. Other people – or organisations – can also act as gatekeepers (e.g. local councils, health organisations, RECs). Their roles could include:

- helping or giving permission for the researcher to approach the community
- assessing the proposed research and considering the overall need, benefit and risks to their community
- helping with education and offering reassurance to participants about the risks
- negotiating on behalf of a community
- participating in study design (including randomisation).

GFBR participants agreed that:

- the role of the gatekeeper can be very important in cluster trials as a way of reaching the community. However, there are unanswered questions about who identifies the gatekeepers, who the gatekeeper should be and whether they have the power of veto over a proposed study.
- gatekeeping can affect the autonomy of individuals participating in trial; they may be overly-encouraged to enroll or told to participate in the research. Since the gatekeeper has power, it can be very difficult for individuals in communities to opt-out or raise concerns.
- on the contrary, the gatekeeper may potentially hinder the process.
- a gatekeeper's "community-level" decision should not replace individual level consent, where this would usually be required. Exceptions might include where the risk profile is low enough so that loss of individual autonomy is outweighed by expected benefit to community.
- researchers must therefore use clear language when communicating with the gatekeeper - not asking for consent.
- the gatekeeper is the entry into the community and can be seen like a first step of community engagement. Engagement with the gatekeeper is not enough - engagement with the wider community should follow.
- it could be a challenge for researchers to coordinate gatekeeper permission across steps and across clusters (e.g. over long time periods where minds change).

Case study 4 reflected these concerns. A SW-CRT was used to test the effectiveness of counseling delivered by community volunteers. One cohort represents 140 to 150 villages and the researchers took permission from a subunit of the cluster (the village head or community leaders or influential community members from every village). The permission was largely to approach the members of that village. The researchers found it a challenging to specify a formal gatekeeper as per the definition in the Ottawa Statement (see Box 2) and were uncertain whether the permission needed to verbal or in writing. They called for more clarity and guidance on these issues.

GFBR participants agreed that as part of their review RECs should assess:

- **the legitimacy of the gatekeeper (which could be as a result of their formal authority to make decisions for the cluster (e.g. administratively or politically) or informally their authority is recognized by the cluster members).**
- **the interests of the different stakeholders and where these may conflict (e.g. institutional vs cluster vs individuals in the cluster). For this they will need to be aware of the social and political setting in society.**

Distinguishing research and implementation: SW-CRTs sit in a position where there is some evidence on effectiveness, but not sufficient. For a SW-CRT to start, more than one existing study is needed to justify the choice of this design (otherwise a conventional RCT is more appropriate). However, if there is sufficient evidence about effectiveness of the intervention arguably this could be moved to full implementation. Sitting between these positions gives rise to questions of whether this is implementation or research (with associated questions regarding the need for REC review etc.).

Regardless of whether you are doing research or scaling up interventions which needs evaluation, a protocol is required. This should be evaluated and there should be some ethical oversight and governance to help to manage the process. This does not mean replicating the mechanism of ethics research review. An example was given of a Canadian ethics screening tool (ARECCI) as a method for helping researchers determine appropriate

oversight for SW-CRTs without requiring everything to go through a REC (avoiding an 'all or nothing' approach). **Participants agreed that we need to find the right body to review these kinds of trials – not just categorise everything as 'research'. The important things is to provide a clear justification for the approach taken (i.e. finding and justifying *appropriate* ethics input).** Also, we need to rethink and build ethics into science to create a genuine partnership throughout the research process.

In quality improvement and public health surveillance, some kind of independent review is sought from departments, methodological review committees etc. However, these tends not to be formally reported so the risks are invisible. Also, many clinical journals will only publish work that has REC approval and so some trials aren't published. GFBR participants agreed that reporting is critical, so outcomes are made available and risks are known.

It was acknowledged that some LMIC countries may not have the infrastructure for reviewing this type of application meaning they will get no scrutiny at all. However, many RECs have a 'minimal risk' category which requires lighter review – this would be one way of providing appropriate ethics input. Some GFBR participants favoured this approach as they were concerned that – if left unregulated – some researchers may try to pass research off as programme evaluation to avoid ethics review.

4. Adaptive clinical trials and platforms

Adaptive platform clinical trials can be designed to investigate multiple therapies, singly and in combination. **Case study 5** described an adaptive platform trial that was designed during the 2014-2015 Ebola outbreak. They incorporate response adaptive randomization (RAR) to improve the ethical balance of the trial from both patient and societal perspectives and to improve the statistical efficiency of the design. Adaptive platform trials are intended to continue beyond the evaluation of any one treatment. The researchers chose this more complex trial design as it can answer more questions efficiently and improve care for patients in the trial by dropping therapies that are shown to be ineffective.

An adaptive platform design might be necessary and/or preferable to an individually randomized CT when:

- the setting is high-risk and time limited, involving complex populations and multiple potential therapies (e.g. outbreak situations, which are more likely to occur in LMICs)
- endpoints happen frequently and quickly (adaptive platforms are not appropriate for long term outcomes)
- the infrastructure (software and algorithms) and knowledge are available.

Case study 5: The design and implementation of an adaptive platform trial for the treatment of Ebola in West Africa

Scott M. Berry, PhD, President and Senior Statistical Scientist, Berry Consultants, LLD

In response to the outbreak of Ebola in West Africa, an adaptive platform clinical trial was designed with the potential to investigate multiple therapies, singly and in combination, and incorporate response adaptive randomization (RAR) to improve the ethical balance of the trial from both patient and societal perspectives and to improve the statistical efficiency of the design. The trial design and preparations were completed, including obtaining REC approval in Sierra Leone, but the trial was not initiated due to the waning of the epidemic. Ethical issues that were considered in the design of the clinical trial and incorporated into the final design include: The trade-off between trial complexity, operational constraints, and trial efficiency; the question of whether the Standard of Care arm was ethically appropriate in the trial and, if the platform trial has been demonstrated to provide better care for patients in the trial as well as provide more efficient answers, how could this be communicated this to the local healthcare providers, review boards, and scientific community?

Adaptive platform trials assess a variety of interventions to see which one produces the best outcome. They respond to data accumulated within the trial to modify their performance – for example by dropping arms that do not perform well and preferentially randomising to the better performing arm as the trial progresses. This is undertaken in a way that preserves the statistical and scientific integrity of the trial. Adaptive models comparing multiple therapies help shift the question from 'does this treatment work?' to 'what is the best way of treating this disease?'. Adaptive platform trial design – and the complex statistical underpinnings – were new to many GFBR participants.

Complexity of design: Case study 5 highlighted the complex tradeoff between trial complexity, operational constraints, and trial efficiency in the Ebola Platform Trial. The more complex trial designs provide the ability to answer more questions efficiently and improve care for participants in the trial, but provided a higher burden to explain to the different research stakeholders in LMICs (e.g. investigators, RECs, regulatory authorities).

GFBR participants agreed it is essential that the characteristics of platform trial designs are effectively communicated to local regulators, RECs and healthcare providers to gain local engagement. This should also help address any misperception that adaptation decreases scientific rigor and efficiency. It is also important to have mechanisms in place to report negative outcomes.

Consent: Case study 6 highlighted the challenges of gaining consent in an emergency situation with critically ill children. A range of potential treatments – with varying risk profiles – were to be included in the adaptive platform trial. In such circumstances, can a one-time consent model be comprehensive enough to achieve the appropriate amount of participant information? And can the adaptive randomization concept be explained in a clear and timely manner? Options being considered include a tiered consent model where participants are enrolled through a waiver of consent, but if they qualify for an intervention deemed more than minimal risk, informed consent could be sought. Another option would be to use a dynamic consent model, where consent is sought and re-sought and research staff are frequently available to answer questions. In low-income settings, this will be logistically challenging, but GFBR participants agreed that ongoing interactions between researchers and participants is vital.

GFBR participants agreed that prospective participants should also be engaged to assess acceptability of platform trials and to ensure meaningful consent. This could involve pre-trial piloting of consenting strategies with volunteers.

Case study 6: Critically ill children and adaptive trials for comparative effectiveness research

Srinivas Murthy, MD MHSc, Assistant Professor, Critical Care & Infectious Diseases, University of British Columbia

This proposed trial, which was in the design phase when presented, would include children with acute respiratory failure and suspected infection, both between and during future outbreaks. The population would be critically ill children admitted to selected intensive care units in North America, Europe, Africa, and Asia. The interventions to be tested were under discussion, but would likely include fluid administration strategies, antibiotic duration, and amount of ventilation support. Ethical challenges include achieving fully informed consent for an adaptive trial in a time-sensitive manner and whether a waiver or model of tiered consent could be appropriate (based on the level of risk). Challenges in relation to the provider-patient relationship were also encountered, especially when faced with the prospect if many aspects of patient care being embedded within a research protocol.

Equipoise: Adaptive trials were described as 'equipoise in action': once there is no longer equipoise the arm is dropped.

Risk and benefits: Poorly performing arms are dropped over the course of the study meaning that the overall benefits and risk of participation are likely to change as the research progresses. This might mean that participants who take place in the early stages take greater risks than participants who enroll later, once the poorly performing arms have been dropped. Issues of fairness may arise if those who are more knowledgeable, better connected, or less sick may delay enrolling in the trial until later when the chance of benefit is higher.

There are benefits associated with shorter trials involving fewer participants where possible/appropriate: an intervention shown to be effective can be made generally available faster; fewer participants are exposed to risks/burdens; lower cost provides opportunity costs for other research/initiatives. These benefits should be taken into account in looking at what is the 'best' trial design for the chosen goals (e.g. in considering when adaptive platform designs are appropriate). Appropriate powering of the study should also be taken into consideration.

Standard of care: The Ebola Platform Trial started with an SoC arm but tested continuously to determine whether the SoC was inferior to any of the other treatment regimens. If SoC was inferior to another treatment, it would immediately be halted in the platform trial and the better treatment would become the new SoC.

REC approval: Case study 5 utilised a master protocol, which can be approved by a REC without the treatments being specified up-front. Under this scheme, it is not necessary to submit a new protocol when the trial data moves the system to another allocation approach. Instead the researcher seeks REC approval for the specific agent as an amendment to the approved protocol.

A REC must be able to assess the statistical claims that are made in an adaptive platform protocol. GFBR participants agreed that this raises questions about REC capacity. It highlights the need for training and support so RECs understand the methodology in order to understand the ethical considerations and issues. **One option might be to have specialised, centralised RECs for adaptive platform trials or for RECs to have (access to) an independent statistician.**

Ethical evaluation of adaptive clinical trials: Mathematical simulation may help provide concrete tools for balancing participant benefit and social benefit through modelling a spectrum of 'avertable risk'. Simulation work has been undertaken to address concerns about response-adaptive randomisation (RAR) and to highlight

the ethical advantages and disadvantages of the approach (Box 1). A variety of clinical trial designs were stimulated – some including RAR and some not – under a variety of epidemic scenarios. The results demonstrated that the advantages and disadvantages (e.g. risk-benefit profile for participants) depend on the specifics of the clinical trial setting and that broad generalisations are not possible. **Clinical trial simulation, when conducted in a manner that is realistic and transparent, can be used to help inform the design, selection, and implementation of innovative clinical trials in LMICs**. Future work needs to be undertaken to assess how these approaches can be improved to make them more available and useful to those working in LMICs. **Simulations could also be an important communications tool that can be used to inform both scientific and lay personnel regarding the characteristics of these trial designs.**

Box 1: Informing ethical evaluations of adaptive clinical trials through simulation

Roger Lewis, University of California

This project conducted extensive simulations of traditional and innovative trial designs (including response-adaptive randomisation) to help illustrate the impact of trial design decisions on the ethical and risk-balance profile from the perspectives of participants and society. Clinical trial simulation, when conducted in a manner that is realistic and transparent, can be used to help inform the design, selection, and implementation of innovative clinical trials in LMICs. Simulations are also an important communication tool that can be used to inform both scientific and lay personnel regarding the characteristics of these clinical trial designs.

5. Controlled human infection models

Controlled human infection models (CHIMs) involve healthy adult volunteers being infected with a well characterised strain of an infectious agent in highly controlled conditions to assess the mechanisms and determinants of immunity. The use of CHIMs has the potential to accelerate the development of vaccines with significant public health relevance, and is useful for identifying promising vaccine candidates suitable for evaluation in large-scale field trials.

Why CHIMs in LMICs? There are ethical and social reasons to conduct CHIMs in countries where diseases are endemic. LMIC volunteers are the 'natural hosts' of disease and differ from HIC volunteers in a number of ways, both in terms of host-pathogen and host-vaccine interactions (e.g. in genetic make-up, previous exposure to pathogen and other infections, immune status, microbiome, and environmental factors). Conducting CHIMs in endemic settings optimizes the drug/vaccine for the populations that are affected by the disease, increasing the likelihood of benefit.

Case study 7 described a CHIM study based in the UK that aimed to develop new vaccines for invasive Salmonella. Although successful, it remained unclear whether findings from challenge studies performed in non-endemic settings can be extrapolated to endemic settings where the burden of invasive Salmonella disease is highest. The case considered the ethical issues associated with establishing the Salmonella CHIM in a LMIC setting.

Case study 7: Control of invasive Salmonella in Africa and Asia – Is there a role for establishing controlled human infection models in endemic countries?

Case presented by Meriel Raymond. Case prepared by Malick M Gibani Oxford Vaccine Group, Department of Paediatrics, University of Oxford

The development of new vaccines for invasive Salmonella can be aided by understanding the human immune response during infection. To address this question and to test the efficacy of candidate Salmonella vaccines, the Oxford Vaccine Group (OVG) at the University of Oxford established a Salmonella controlled human infection model (CHIM) in UK healthy adult volunteers. It is recognised, however, that volunteers in endemic countries are likely to differ from UK volunteers across a range of important variables. These issues are particularly pertinent for invasive non-typhoidal Salmonella disease, where chronic-malaria, sickle-cell disease, malnutrition and HIV infection represent major risk-factors. For findings from challenge studies to inform vaccine development, it may be necessary to validate findings in endemic settings where vaccines will ultimately be deployed. If this CHIM was to be employed in LMIC setting the ethical issues associated with model would need to be considered in this context: participant safety and benefit; risk of transmission; volunteer reimbursement; engagement with local REC and regulatory authorities and requirements.

Resource requirements and safety: **Case study 7** demonstrated the significant resources requirements of a CHIM (in this case for salmonella, conducted in a HIC). Recruitment involved telephone screening, provision of written information, clinic visit and screening including General Practitioner input. The research phase incorporated daily visits for 14 days; emergency contact and home visit if necessary; access to in-patient facilities if needed; remote monitoring via e-diary; checks each night by an on-call doctor and 24/7 access to study team. The challenges of translating this to LMICs include: less infrastructure; more pressure on staff who are already over-worked; a significant laboratory burden; increased risk of disease severity; a higher likelihood of having volunteers with significant past health conditions and less access to primary healthcare records. **GFBR participants agreed that a key requirement is that the safety measures need to be as least as stringent as the HIC CHIMs model. For this, there needs to be good clinical and laboratory facilities, careful monitoring and good governance.**

Consent: Several factors could hamper consent e.g. cultural understanding of germ theory and misunderstanding of probabilities. However, **case study 8** – a social science study embedded in a LMIC CHIMs for malaria – showed participants had a good understanding of the aims of the study. As the CHIM was taking place in a malaria endemic area, participants had a daily life comparator and understood they would get malaria and that it is curable.

Case study 8: Experiences and perceptions of study participants in a malaria challenge study in Kilifi, Kenya

Dorcas Kamuya, KEMRI-Wellcome Trust Research Programme in Kilifi, Kenya

A Controlled Human Malaria Infection (CHMI) study in Kenya aimed to assess human immunity to Plasmodium falciparum using sporozoites (PfSPZ Challenge) administered by direct venous inoculation. The study was expected to recruit 200 individuals across three challenge events. A social science study was embedded in the 2nd challenge event which screened 114 participants and enrolled 64 (49 male; 15 female). The social science sub-study aimed to explore participant' experiences, their understanding of the malaria challenge study, and motivations for participation. Areas for ethical consideration emerged, including: perceptions of risks; the importance of community engagement to address misperceptions; and ensuring there is an appropriate balance of risks and benefits for participants and for communities.

Risk and benefit: It is important to ensure participants understand the associated risks (including a clear explanation of the probabilities and the fact they have a real chance of getting sick). The degree of risk – both real and perceived – will vary according to the CHIM study. For example, depending on how well the disease characteristics are understood (e.g. malaria vs Zika). The participants cited in **case study 8** were willing to be infected with malaria but un-prompted said they would not participate in a HIV study.

GFBR participants recognized the need to think how **financial incentives** (e.g. payment for time off work and inconvenience) would translate into a LIMC setting, without becoming undue inducement. Concern was expressed about the potential to attract the under-privileged in society and to create a 'professional participant', in addition to creating potential tension in the communities (why one person was chosen rather than another). Researchers need to be alert to what other things participants perceive as a benefit, beyond any immediate health benefit (e.g. health screening that wouldn't otherwise be available). In the context of LMIC vaccines research there's an additional benefit in that the treatment might be protective.

Transmission risk: The CHIM in **case study 7** took place in the UK where the risk to third parties was reduced due to good sewage systems, strict rules about hygiene, and advice to those sharing houses (including screening where necessary). The research team had an arrangement with the police to find participants who went missing during the CHIMs study, given their risk to public health. Given the more limited resources in LMICs the risks of transmission are magnified. **Case study 7** used an outpatient model but it is questionable whether this would be appropriate and acceptable in a LMIC. In contrast, **case study 8**, involved long inpatient stays. While this was necessary to clear infection and provide treatment, it clearly compromises the participant's right to withdraw from the research.

It is important to ensure that people have the freedom to withdraw like with any other study but are not a risk to themselves or their communities. It should be made clear in the information sheet that if people were to withdraw they would need to be treated and cleared of the infection before they could return to their communities – a form of conditional withdrawal.

Case study 9 presented the deliberations of an expert panel on whether a Zika virus CHIM could be ethically justified. Uncertainty regarding length of infection (some people appeared to fail to clear the virus), risk of third party transmission (to sexual partners and fetuses) and uncertain long term effects outweighed the potential social value and acceptability of the study. While such a study could be ethically acceptable, the panel concluded that the conditions are not currently met.

Case study 9: The case of Zika virus human challenge studies

Ricardo Palacios Gomez, Butantan Institute, Brazil and Seema Shah, Seattle Children's Research Institute and the University of Washington, USA

In 2016, researchers proposed to conduct a human challenge trial (HCT) in which healthy volunteers would be intentionally exposed to Zika virus. The proposed Zika virus HCT equally aimed to learn more about the early stages of Zika infection and efficiently test whether vaccines can protect against Zika infection through intentional infection of healthy individuals. The trial was to be conducted in non-endemic settings and enrol healthy volunteers who would not otherwise be exposed to Zika virus. As the potential funders of such a trial, the National Institute of Allergy and Infectious Diseases and the Walter Reed Army Institute of Research felt this proposal was ethically complex and assembled an independent, multidisciplinary expert panel to address the ethical issues involved. Amongst other things, the Panel considered what the upper limit of risk in research should be, how risks to bystanders can be justified, and whether it is better to conduct an HCT in endemic or non-endemic settings. The Panel concluded that a Zika virus HCT could be ethically justified in principle, but would be premature at the time.

Public acceptability and maintaining public trust: GFBR participants from a number of countries could not envisage CHIMs studies being accepted in their setting. **This speaks to the need for empirical research with communities and regulators to find out what is acceptable and important to local communities, as well as engagement to enhance understanding of these studies.** There is often mistrust of researchers coming from different countries, with communities having a sense that they are being 'used' for their data. CHIM studies in LMICs would likely attract intense scrutiny and real risk to reputation of the research centre if anything went wrong (whether it was directly related to the study or not). This can have detrimental effects for an institution and trust relationships.

6. Guidance, regulation and capacity development

An overview of international guidance was presented at the meeting (Box 2) with responses from a panel offering a range of regional perspectives (from East Africa, the Caribbean, Latin America and Southeast Asia). GFBR participants also heard about a funder initiative to create CHIMs guidance.

Box 2	Overview of international guidance
Cluster Randomised Trials	**The Ottawa statement on the ethical design and conduct of CRTs** (2012) aims to provide researchers and RECs with detailed guidance on the ethical design, conduct, and review of CRTs. The Statement sets out 15 recommendations that provide guidance on the justification of CRTs; independent ethics review; identifying who is the research participant; obtaining informed consent; role of gatekeepers in protecting group interests; assessing harms and benefits and protection of vulnerable participants. **The Council of International Organizations of Medical Sciences (CIOMS)** guidelines 2016 also addressed CRTs, stating that researchers need to address specifically: who is the research participant; informed consent (is it feasible and required and from whom?); whether informed consent invalidates results; ethical acceptability of no-intervention group, in particular in low income settings and gatekeeping.

	There are no significant differences between the Ottawa statement and CIOMS, other than status and focus (the former a position statement focusing on CRTs and the latter international ethical guidance focusing on what is different in CRTs in comparison to other studies). Both Ottawa and CIOMS have limited guidance on specific protection in the case of CRTs conducted in LMICs.
Stepped wedge CRT	There is no specific guidance in SW-CRTs but both **Ottawa** and **CIOMS** contain indirect guidance. The ethical issues have been articulated in a number of research papers, which drew out issues with informed consent, clinical equipoise, social value and when SW-CRT are – and are not – considered research and subject to REC review.
Adaptive platforms	There is no guidance or regulation but again some research papers articulate the ethical issues e.g. implications for informed consent if master protocols last for many years and the role of RECs in assessing these complex designs that involve real-time decision making.
CHIM	The **WHO 'Human Challenge Trials for Vaccine Development: regulatory considerations'** (2016) addresses a number of issues including whether/how studies are regulated (e.g. whether they are considered investigational medicinal products); social and scientific value; minimizing risk/maximizing benefit – to both the participants and society; 'truly' informed consent; complexity of risks and informed consent and that CHIMs should not involve children/incompetents, except if the challenge organism is a licensed live, attenuated vaccine; the need for independent ethics review. '**A framework for CHIM studies in Malawi**' by Gordon et al is based on a Wellcome workshop on CHIM in Low Income Countries held in Blantyre, Malawi in 2017. It offers a framework for considerations of CHIM in Malawi including that the research focuses on an issue of national importance; it promotes capacity development in-country; there's a strong scientific case (with no alternative approach); model quality is established by published data; safety is already demonstrated and governance structures are in place. The funder Wellcome is in the process of developing an **ethical framework for CHIMs**. This is part of Wellcome's priority areas on Vaccines, which aims to speed up vaccine development where this is ethically and socially acceptable and possible. The framework will be informed by an evidence review of previous CHIM studies in LMICs (Thailand, Kenya, Tanzania, Gabon) and engagement with relevant communities. Wellcome will work with other funders to agree principles while recognising these need to be implementable.

There is limited international guidance on these trial designs and scarce guidance specific to LMICs. Some GFBR participants called for international and LMIC specific ethical guidance on use of these designs and argued that uptake will be dependent on international organisations issuing the guidance and taking the lead. Having this guidance should avoid 'precautionary' approaches being taken by RECs and regulators rejecting any kind of novel design in many countries. Other GFBR participants – including several of the regional panel respondents – were less convinced by the need for new guidance and instead placed the emphasis on the need for local training and education, especially of RECs.

Capacity was raised throughout as a major constraint in the adoption of novel designs: How can researchers, regulators, ethics committees be better supported with respect to understand the facets of these novel

designs? This includes them being able to digest the scientific aspects – risk, bias, power calculations, limitations and strengths – but also to better discern the key and emerging ethical issues in such approaches. This need is particularly pressing for adaptive trials as complex mathematical simulation are increasingly being used as a tool for assessing risk and benefits within a trial design.

GFBR participants recommended that:

- **capacity needs to be built at the country/region level before novel approaches are deployed, and this should be reinforced by continuous engagement e.g. fora for researchers, ethicists, and statisticians to meet regularly at the regional and local levels.**
- **there is a need for qualitative research with regulatory bodies and RECs to find out what they think and their attitudes/concerns regarding novel designs.**
- **funders can help by including additional provision for training/support of LMIC RECs, attached to specific projects, to enhance their confidence to assess novel trial designs.**
- **investment is needed in continuous professional development and in teaching innovative designs (i.e. broader educational initiatives rather than training tied to a project). This could raise awareness of the good scientific reasons why these studies are appropriate (e.g. when some CHIM studies might need to take place in LMICs). International organisations such as WHO or PAHO could provide this training.**
- **local RECs could set up relationships with researchers and/or RECs in HICs who are more experienced and knowledgeable in these types of trials and methodology. LMIC RECs, who have expertise in local culture and context, could send their protocols and work together with HIC colleagues to identify ethical issues and how to overcome them. However, there was some concern about setting up these types of relationships and how to ensure that the role of the REC in HIC is not interpreted as or does not become prescriptive.**
- **there is a need to engage LMIC regulatory bodies, especially for CHIMs.**

Annex 1: Background information on GFBR and meeting content

The Global Forum on Bioethics in Research (GFBR) is the principal global platform for debate on ethical issues pertaining to international health research. Its core aims are to give voice to low- and middle- income country (LMIC) perspectives in debates about global health research ethics and to promote collaboration.

The Forum meets annually to address a specific topic in research ethics and is case study based. This approach enables participants to understand the practical issues "on the ground" in addition to broader ethical and policy questions. Up to 100 participants are selected for each meeting through a competitive process. Participants come from a diverse range of disciplines, countries and career stages and awards are available to LMIC colleagues to cover travel and accommodation.

Twenty case studies were submitted for this meeting, along with 10 guidance and policy papers. A further 52 applications were received from potential participants. Nine cases studies and one policy paper were selected for oral presentation (see insets throughout the report). Several of the other case studies and policy papers were presented at the meeting in the form of posters or short Pecha Kucha presentations:

Pecha Kuchas

1	**Shivaprasad Goudar, India** Alternative clinical trial designs for research on hypertensive disorders of pregnancy in low resource settings
2	**Steven Bellan, USA** A quantitative framework for balancing ethical tradeoffs in vaccine study design during highly fatal, emerging infectious disease epidemics
3	**Khine Zaw Oo, Myanmar** Ethical issues of alternative clinical trial designs and methods in Myanmar
4	**Vina Vaswani, India** Alternate to clinical trial design for Ayurveda in chronic non-communicable diseases, in non-emergency settings
5	**Hany Sleem, Egypt** Paving the way: Better understanding of the Egyptian research ethics committees, and regulatory authority for alternative clinical trial designs
6	**Gibril Ndow, Gambia/UK** Ethics of alternative clinical trial methods in LMIC research: The Gambia Hepatitis Intervention Study experience (GHIS)

Posters

1	**Jackeline Bravo, International Center for Medical Research and Training, Colombia** Implementation of the Clinical Practice Guidelines (CPG) for the Elimination of Maternal Child Transmission (ETMI) of Syphilis / HIV, Colombia
2	**Nderitu Wanjeri, Egerton University, Kenya** (In)adequacy of the guidelines and policies in addressing alternative clinical trials in Kenya
3	**Jeremy Sugarman, Berman Institute of Bioethics, USA *et al.*** Developing participant safety plans for research involving network randomization and stigma
4	**Steven Bellan, University of Georgia, USA *et al.*** A quantitative framework for balancing ethical tradeoffs in vaccine study design during highly fatal, emerging infectious disease epidemics
5	**Sarah JL Edwards and Charlie Norell, University College London, UK** Reconciling controversies over study design during Ebola and international harmonisation of regulatory requirements: a work package for the EDCTP
6	**Munario Dimairo, Sheffield University, UK *et al.*** Journeying through the development of a consensus-driven adaptive designs reporting guidance
7	**Rachel Greer, Mahidol-Oxford Tropical Medicine Research Unit, Thailand** Implementation of CRP point of care testing in primary care to improve antibiotic targeting in febrile and respiratory illness (ICAT)

Annex 2: List of abbreviations

GFBR: Global Forum on Bioethics in Research

LMIC: Low- and middle-income country

HIC: High income country

REC: Research ethics committee

RCT: Randomised controlled trial

RAR: Response adaptive randomisation

CRTs: Cluster randomised trials

SW: Stepped wedge

CHIMs: Controlled human infection models

SoC: Standard of care

PAHO: Pan American Health Organization

CIOMS: Council of International Organizations of Medical Sciences

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Full case study write-ups are available on the GFBR website.

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