

Background paper: the ethics of alternative clinical trial designs and methods in low- and middle- income country research

Meeting in Bangkok, 28-29 November 2017



Purpose of the document

Increasingly the conventional individually randomised controlled trial (RCT) is being replaced by alternative clinical trial designs and methods in low and middle income country (LMIC) research. The purpose of this paper is to map out some of the key ethical issues associated with these designs and methods to prepare for participation in the 2017 Global Forum on Bioethics in Research (GFBR) meeting. The document outlines the scope of the meeting theme and covers the following areas:

1. Introduction and context
2. Adaptive trials
3. Cluster randomized trials
4. Stepped wedge trials
5. Controlled human infection models
6. Current guidelines on alternative trial designs and methods

There is a significant body of literature on alternative designs such as adaptive trials in high income countries (focusing more on the statistics and methodology and less on the intertwined ethical issues). Scant literature exists, however, on the use of these designs in LMICs despite their current and increasing use. The upcoming GFBR meeting will be situated in the context of LMICs and provide an opportunity for a range of stakeholders (e.g. bioethicists, clinical trialists, biostatisticians, policy-makers) to engage in rigorous critical assessment through discussion of real-life LMIC case studies.

This paper is being published with the call for case studies and proposals on guidance and policy issues. Case studies and proposals may relate to the designs mentioned below or other alternative designs and methods¹ that present ethical challenges. In general, they should focus on research in LMICs² and could address (but are not limited to) one or more of the following questions:

- Under what circumstances and why is an alternative design or method ethically preferable to a conventional RCT in the context of research in LMICs?
- What benefits do alternative designs and methods (such as adaptive trials) offer LMIC participants in comparison to RCTs and how do they compare in terms of acquiring information for the general clinical community?
- What are the opportunities and barriers for implementing alternative designs and methods in LMICs?
- What makes alternative trial designs and methods ethically challenging (or better) in LMICs?
- What are the ethical and practical issues of alternative designs and methods. Are these factual or assumed?

¹ For example, multi-staged approach, basket clinical trials, cohort multiple randomised trial.

² However, we do not want to exclude case studies from high income countries if there could be valuable lessons to learn, and some parallel or relevant ethical considerations, for example, this may include adaptive trial design with indigenous populations in countries like Australia and Canada. Please see the call for case studies and proposals for further details.

- How should investigators explain complex information to a prospective participant to ensure that they understand the alternative trial design before enrolling?
- How best can investigators engage with local communities to assess acceptability (for social, cultural, political or ethical reasons) of the study design?
- Under what circumstances/criteria would the conditions be satisfied for providing a waiver on individual consent during a cluster-level interventions?
- How well are alternative trial designs and methods understood by different research stakeholders in LMICs (e.g. investigators, research ethics committees (RECs), and regulatory authorities)? How can local RECs and regulatory authorities be supported to better understand and evaluate these complex trials?
- What are the governance and regulatory needs and how can these be addressed (e.g. through the development of design-specific guidance)?
- Can guidance help to address some of the ethical challenges and if so, what form should these take and what should they include?

1. Introduction and context

Individually randomized controlled trials (RCTs) are the conventional method for evaluating the efficacy and safety of new therapies in humans. However, standard RCTs are very expensive and very slow (especially phase III), and may not be feasible in some research contexts such as the recent Ebola outbreak (Caplan, Plunkett & Levin, 2015; Lanini et al., 2015). Consequently, there has been considerable interest by the pharmaceutical industry and regulatory agencies such as the European Medicines Agency (2004) and Food and Drug Administration (2010) to use other more efficient trial designs, the best known of which are called adaptive trials. Other alternative trial designs, for example, cluster randomized trials and stepped wedge trials are part of the movement that seeks to evaluate interventions/treatments in real-world conditions. These designs, which involve randomisation on a group level rather than an individual level, offer certain practical and logistical advantages that can help simplify trial organization and fieldwork in low resource settings.

Study design was a key consideration of the WHO Ethics Working Group during the Ebola outbreak in 2014. The report of the Group's discussion provides a valuable summary of the issues to be considered by investigators, ethics committee members, decision makers and other stakeholders in developing ethically acceptable and scientifically sound studies during the Ebola outbreak (WHO 2014). Regarding trial design, the report states that 'Conducting individually randomized controlled trials with a control comparator (other than placebo) may not be acceptable to the local community if the control arm does not include a potential therapeutic intervention (even if it is not previously tested) beyond standard/supportive care; In this context, an adaptive trial design that has the capacity to yield meaningful and interpretable data quickly in the midst of the (Ebola) epidemic might be considered as preferable. An adaptive design could include elements of randomized controlled trials, cluster randomization, stepped wedge, and single arm comparison trials.' Having been proposed and /or used during Ebola outbreak, these designs are becoming more familiar as alternatives to the conventional RCT (Doussau & Grady, 2016; Lanini et al., 2015). However, there has been insufficient debate on how broadly applicable the use of the designs may be (beyond the context of public health emergencies) as a more ethical alternative to the conventional RCT.

Other methods are also increasingly being used in LMICs, for example Controlled Human Infection Models. Performing these studies to test vaccine efficacy in endemic populations has the advantage of ensuring that safe and effective doses of vaccines are used in these populations, which might be different from doses used in more naïve populations (Bodhidatta et al 2012).

While alternative clinical trial designs and methods offer a number of potential advantages in a LMIC settings, 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, RECs and regulators with little support in how to evaluate, implement and run these often complex trials.

The choice of study design and method will be informed by an ethical analysis of the options, including with respect to autonomy and consent, equity and risk/benefit evaluation. Ideally trials would achieve the best outcome for participants (reduced risk and enhanced benefits) within the constraints of getting the best scientific outcome to produce benefits for society. Another important concept is clinical equipoise, which serves as an indicator that participants in two trial arms will be treated in a comparable way with respect to the risk/benefit of the treatment they are receiving as there is genuine clinical uncertainty about the merits of each arm. There is an extensive literature on whether or not clinical equipoise is a requirement for clinical research (Freedman, 1987 and Miller and Brody, 2003). Rather than rehearsing these debates the GFBR meeting aims to look at practical examples of alternative trial designs and methods that are being used in LMICs while recognizing that how the ethical and scientific issues are framed is tied to how concepts such as equipoise are understood.

2. Adaptive trials

Adaptive trials allow modifications to the trial and/or statistical procedures of the trial after its initiation without undermining its validity and integrity (Lang, 2011; Saxman, 2015). Some of the common adaptations include modifications to sample size, treatment allocation and the addition or deletion of treatment arms (Chow, 2014; Lin et al., 2016). The envisioned objectives for such adaptive trials include reduction in sample sizes, duration or cost of the trial, improvement of the treatment of trial participants and enhanced trial accuracy or conclusions about the effectiveness of treatments (Brown et al., 2016; Kairalla et al., 2012).

One common example of an adaptive trial design is the outcome-randomized or response-adaptive trial which typically begins by randomizing participants on a 1:1 basis to either the treatment or control arms of the trial. Thereafter, as initial participant-response data accumulates, the allocation ratio is modified in favour of the better-performing arm (Lee, Chen & Yin, 2012). This implies that more participants enrolled in the later stages of the trial will have a higher probability of being allocated to the better treatment – and this raises ethical concerns about justice and fair participant selection (Hey & Kimmelman, 2015). Recently, Berry et al. (2016) described a practical case-study of an outcome-adaptive randomization design for use in the context of Ebola research in Sierra Leone. In another example, researchers of the PanACEA (Pan African Consortium for the Evaluation of Antituberculosis Antibiotics) recently conducted multi-arm multi-stage (MAMS) phase II TB clinical

trials that utilize adaptive designs in South Africa and Tanzania. These trials tested four different treatment arms simultaneously within a single trial, and used interim data analysis to rapidly identify and drop interventions that were not effective (Boeree et al., 2017).

Example of an adaptive design: 'Creative solutions to extraordinary challenges in clinical trials: methodology of a phase III trial of azithromycin and chloroquine (AZCQ) fixed-dose combination in pregnant women in Africa' Chandra et al., 2013

Malaria in pregnancy is one of the most common preventable causes of maternal and neonatal morbidity and mortality in sub-Saharan Africa. The WHO recommends use of intermittent preventive therapy in pregnancy (IPTp) alongside curative measures (e.g. bed nets) to manage the spread, but parasite resistance is growing to Sulphadoxine-pyrimethamine (SP) the standard for IPTp in several countries. This paper describes a trial that compares SP-IPTp with a potential replacement, AZCQ- IPTp. The trial was designed to meet stringent regulatory agency scientific advice and IPTp policy makers' recommendations, and incorporated an innovative adaptive design to maintain proper operating characteristics and to minimize any undue exposure of the pregnant women to study drugs by optimizing sample size estimation and through interim checks of the data. The trial was sponsored and conducted by Pfizer Inc, co-funded by Pfizer Inc and the Medicines for Malaria Venture and had oversight by an independent external data monitoring committee with three-quarters membership from sub-Saharan Africa.

2.1 Ethical issues in adaptive trial designs

While there is growing interest in adaptive trials, important ethical issues are raised by such designs (Laage et al., 2016). In fact, some commentators have been critical of the argument that adaptive trials offer any ethical advantages over standard RCTs (Begg, 2015; Hey & Kimmelman, 2015). A widely recognized ethical framework developed by Emanuel, Wendler, Killen and Grady (2004) is used here to discuss some of the ethical issues in adaptive trials.

Informed consent: Informed consent is a central ethical tenet in clinical research necessitating that participant information be clearly explained and understood. However, several empirical studies have suggested that most clinical trial participants do not understand complex clinical trial terminology such as randomization (Ndebele et al. 2014), let alone in adaptive trial designs (Hey & Kimmelman, 2015). For instance, in outcome-adaptive randomization, the informed consent process would need to clearly explain to prospective participants that, as preliminary trial data accumulates, their chances of being allocated to a superior treatment are likely to increase, and participants would also need to understand that there still remains a significant chance for them to be randomized to the inferior treatment. Will participants understand that they are participating in research in which they may still be randomized to an inferior treatment even if interim data analysis shows evidence of a potentially superior treatment? How should the investigator explain such complex information to a prospective participant to ensure that they fully understand before enrolling in an adaptive randomized trial (Joffe & Ellenberg, 2011; Legocki et al., 2015; Saxman, 2015). Furthermore, although not unique to adaptive trials, concerns has been expressed that adaptive randomization may exacerbate therapeutic misconception – that is, participants may enrol into the trial believing that they would receive the best-possible treatment for their health

condition, thus failing to distinguish between clinical research and clinical care (Meurer, Lewis & Berry, 2012).

The WHO Ethics Working Group on the Ebola outbreak recognised informed consent as an important ethical requirement. The Group recommended that 'the consent processes must be adapted to contextual limitations. Innovative approaches may need to be considered to ensure comprehension and voluntariness. These could include video or audio recordings or, in some cases, surrogate consent' (WHO 2014).

Fair participant selection: In outcome-adaptive randomization, as trial data becomes available favouring one treatment arm over the other, modifications may be made with incoming participants more likely to be assigned to the better-performing treatment (Berry et al., 2016). Participants may deliberately prefer to enrol into the trial later. This raises ethical concerns about fair participant selection or justice – which requires that no individual should unfairly bear the risks/burdens over the other. In other words, participants who enrol later in the trial are more likely to receive the better treatment (hence receive more therapeutic benefit) than participants who enrolled earlier, thus causing the latter to assume more risks and burdens than the former (Saxman, 2015; van der Graaf, Roes & van Delden, 2012).

Scientific validity: Some commentators argue that adaptive designs may undermine the scientific validity of the trial (Hey & Kimmelman, 2015; Joffe & Ellenberg, 2011; Pullman & Wang, 2001). For instance, some of the scientific concerns about adaptive trials include 1) control of type I error rate; 2) the minimisation of impact of any adaptation-associated statistical or operational bias on the estimates of treatment effects; and 3) the real interpretability of the results (Menis et al., 2015).

During interim analysis of accumulating data, an ethical dilemma may arise regarding whether to withhold such information from participants (in order to maintain scientific integrity) or to disclose the information to participants – which might compromise the scientific integrity of the trial (Laage et al., 2016; van der Graaf, Roes & van Delden, 2012).

Favourable risk/benefit ratio: An ethical advantage of the outcome-adaptive trial design is a favourable risk/benefit ratio (Legocki et al., 2015; van der Graaf, Roes & van Delden, 2012). In other words, as participant-response data accumulates, incoming participants have a higher probability of being randomized to the superior arm, thus maximizing the number of participants receiving the better treatment and minimizing those receiving the inferior treatment. However, some critics argue that adaptive randomization generally does not enhance favourable risk/benefit ratio (Hey & Kimmelman, 2015) and that it is "inferior to 1:1 randomization in terms of acquiring information for the general clinical community and offers modest-to-no benefits to the patients on the trial" (Korn & Freidlin, 2011).

Clinical equipoise – defined as a state of genuine uncertainty regarding the therapeutic merits of each arm in a trial – is part of the risk/benefit circulus. On the one hand adaptive designs minimise the number of participants exposed to the inferior arm; on the other hand, clinical equipoise may be lost as data accumulates. Generally, it is considered ethical to randomize participants to either arm

of a trial insofar as equipoise holds but unethical once it is lost (Hey & Kimmelman, 2015; Saxman, 2015).

Independent ethics review: Adaptive trial design protocols are generally complex and this has implications on research ethics committees (REC) and other regulators who are mandated to review and approve such studies – they will need to be knowledgeable and have the necessary scientific expertise in adaptive trial designs (Pullman & Wang, 2001). This will imply the need for enhancing REC capacity for scientific and ethical review of such adaptive trials designs.

Limited resources and infrastructure: More resources and infrastructure are required for planning and coordinating adaptive trial designs. Generally, the lack of adequate infrastructure and resources to implement such designs might act as a barrier particularly in poor-resource settings.

2.2 Utility of adaptive trials in low and middle income countries

Adaptive trials have the potential to improve the development of new therapies in less developed countries, for example in Ebola research in Africa, where standard RCTs may be unethical and unfeasible (Lanini et al., 2015). Adaptive trials have also been reported to provide practical solutions for improving the treatment of tuberculosis in high-burden TB countries such as South Africa (Boeree et al., 2017; Davies et al., 2015; Phillips et al., 2012). Recent systematic reviews have reported a relative increase in the use of adaptive trial designs. However, the data suggests that most of these adaptive trials have only been conducted in high-income countries, for example US, Canada, UK and Europe (Dzimairo et al., 2015). Some of the operational and practical barriers for using adaptive trials have been well reported in the literature (Coffey et al., 2012; Kairalla et al., 2012).

Methodological issues

- Adaptive trials are more complex than standard RCTs (in terms of the design, analysis and conduct) and have the potential to complicate statistical analysis and inferences thus having implications on the accuracy of conclusions derived from the trial (Freidlin & Korn, 2014). A primary statistical concern with adaptive trials is the potential to inflate the type I error especially in confirmatory adaptive clinical trials (FDA, 2010). Investigators may be reluctant to develop proposals involving adaptive trial designs in order to avoid rejection by regulatory authorities.
- Adaptive trials may be appropriate in situations where the study endpoints can be evaluated early/quickly. For example, during the Ebola outbreak when indications early in the epidemic projected thousands of cases weekly which would have been a large enough sample size to carry out several parallel trials. Conversely, adaptive trials may not be suitable in settings where the primary endpoint can be observed only after long-term follow-up (Lanini et al., 2015).

3. Cluster randomized trials

A cluster randomized trial (CRT) design involves the randomization to an intervention of groups or cluster units rather than independent individuals. For example, communities could be selected as the unit of randomization in a CRT evaluating the effectiveness of a vaccine in an LMIC.

Practical advantages of cluster randomized trials

- It offers more logistical and administrative convenience in settings where allocation of the intervention is challenging due to resource or financial constraints.
- It minimizes the risk of “contamination” – whereby participants randomized to the control arm may be exposed to the intervention via interaction with individuals assigned to the intervention arm, thereby resulting in biased results on the effect of the intervention (DHHS, 2014).

Methodological issues

- CRTs present methodological challenges during the design and analysis stages. CRTs are more methodologically complex and less efficient statistically compared with standard RCTs. Furthermore, CRTs are prone to many sources of bias. Therefore, investigators need to explicitly justify using cluster randomization instead of individually randomized trials (Taljaard et al., 2013; Weijer et al., 2015).

Example of a CRT: ‘The ring vaccination trial: a novel cluster randomised controlled trial design to evaluate vaccine efficacy and effectiveness during outbreaks, with special reference to Ebola’ Ebola çá suffit ring vaccination trial consortium 2015

One approach to communicable disease control is ring vaccination of individuals at high risk of infection due to their social or geographical connection to a known case. This paper describes the protocol for a novel cluster randomisation control trial of immediate versus 21 day delayed ring vaccination against Ebola in Guinea. The authors summarise that a ring vaccination trial tracks the epidemic, recruiting individuals at raised risk of infection due to their connection to a case: this design may both contribute to transmission interruption and have a higher power to detect vaccine efficacy than other study designs. In a ring vaccination trial, the control arm could be a placebo or a vaccine against a disease not under study but this was deemed unacceptable in Guinea because of national and international concerns about leaving vulnerable individuals unprotected when a potentially effective vaccine was available.

3.1 Key ethical issues in CRTs

Informed consent: CRTs present a unique ethical challenge to the informed consent process. In cluster-level interventions, refusal of consent by individuals in that cluster may be meaningless. Furthermore, randomization of clusters can occur before individual cluster members can be identified or approached for informed consent. If the unit of randomization is a very large cluster, e.g. entire communities, obtaining individual consent before randomization can be logistically complex, if not almost impossible. RECs may need to waive the requirement for consent; cluster-level interventions are the most common case for the use of such a waiver.

Who counts as the participant?: CRTs also raise ethical questions regarding who counts as the research participant and who should provide consent. For example, in a CRT evaluating new handwashing technique, the unit of randomization (e.g. healthcare facility with practitioners) may differ from the unit of outcome measurement (e.g. patients), and so there needs to be clarity about who is the research participant and who, when and how will consent be provided for what (McRae et al., 2011).

Role of gatekeepers: The role and authority of gatekeepers to provide permission to enroll clusters in a CRT is another key ethical issue (Gallo et al., 2012). While gatekeepers may play an important role in protecting group and institutional interests, they cannot provide proxy consent on behalf of individual research participants (Weijer et al., 2015).

Assessing risk/benefits: Randomization of clusters rather than individuals has important implications, not only for individuals, but for the entire cluster or community. This raises ethical questions about how to assess the potential risks and benefits beyond an individual to ensure that the entire cluster(s) or community is protected from potential risks (e.g. social stigmatization) associated with their participation in the CRT.

Protection of vulnerable participants: Some research participants (e.g. employees, people within hierarchical institutions) within randomized clusters may be unduly influenced to participate in CRTs, and not be able to freely refuse or withdraw participation in a CRT. There is need for additional measures to identify and protect the interests of vulnerable populations (Weijer et al., 2015).

Inequality and fairness: On one hand cluster randomised trials may be designed in such a way that they are more socially acceptable, for example by clustering rather than randomising within a family or treatment centre. On the other hand, allocation of interventions by clusters may raise concerns about fairness and could potentially exacerbate inequalities among groups of people (Conrad & Edwards, 2011) and disturb communities creating social disharmony (Lignou et al., 2016).

4. Stepped wedge trials

Stepped wedge trials are designed to allocate an intervention to study participants or clusters at different predefined intervals. Stepped wedge designs offer a practical solution in resource-limited settings where it is difficult to allocate the intervention simultaneously to all, or when there is a desire to study the roll-out of an intervention within a health system (Doussau & Grady, 2016).

Example of a stepped wedge design: 'The Gambia Hepatitis Intervention Study' The Gambia Hepatitis Study Group 1987

The Gambia hepatitis intervention study used a stepped wedge cluster randomised design to investigate the effectiveness of a vaccine for hepatitis B (HBV) in preventing liver disease. It began in 1986 with the intention of setting up a national surveillance system to detect new cases of hepatocellular cancer and other chronic liver diseases over a period of 30 to 40 years. This paper describes the trial and the several factors that affected the final decision on trial design: '(a) the expense of the vaccine and its limited availability prohibiting immediate universal HBV vaccination; (b) the desirability of having comparison groups available from the same time period; (c) the severe logistic difficulties that would have been encountered with randomization at the individual level in a trial of this magnitude, with a large number of immunization teams working under field conditions and with four vaccine doses per individual being required. Individual randomization might also have appeared ethically questionable; (d) the hope that HBV vaccine would be widely available at the end of the study and that by that time a nationwide delivery system should be in place.'

4.1 Ethical issues in stepped wedge designs

Clinical equipoise: In most cases, stepped wedge designs are implemented in situations where there is some prediction that the intervention will do more good than harm or the prior knowledge indicates that harms are minimal to expected benefits. This creates an ethical issue because there may be loss of clinical equipoise (genuine uncertainty about the merits of each of the treatment arms), yet equipoise is generally considered an important requirement when randomizing participants. Furthermore, delaying the intervention to participants in the control group until it is their turn to be allocated the trial intervention raises ethical concerns (Prost et al., 2015).

Benefit to participants: Proponents of stepped wedge designs argue that there is an ethical advantage in that all clusters receive the intervention, although at different time points – a clear benefit especially when the intervention is likely to do more good than harm (Prost et al., 2015). However, in a recent paper, Doussau and Grady (2016) argue against the notion that all participants receive the intervention in stepped wedge designs as being incorrect and misunderstood. In their view, while all clusters receive the intervention, it does not mean that all individuals within those clusters will receive the intervention. For example, if the cluster is intensive care units, patients may be admitted and discharged before the unit crosses to the study intervention.

Consent: The informed consent process needs to clearly explain information about who will access the intervention – because not all stepped wedge designs allocate the experimental intervention to every participant (Doussau & Grady, 2016). Further, there needs to be clarity about who will provide informed consent (individuals, community). A waiver of consent may be appropriate in some cases, particularly those in which there is a cluster-level intervention.

Methodological issues

- Stepped wedge designs (like adaptive designs) are complex and challenging and therefore require rigorous methodological support throughout all the trial stages of implementation and data analysis in order to ensure scientific validity.
- There is also high risk of bias, attrition and loss of statistical power associated with stepped wedge designs (Kortz et al., 2012).

5. Controlled human infection models

Controlled human infection models (CHIMs), also known as human challenge models, involve intentionally infecting healthy volunteers with a pathogen as part of the trial design, in order to assess the efficacy of new vaccines and drugs (WHO, 2016). The models may aid in detecting promising vaccine candidates prior to trials involving hundreds or thousands of people, either by the early elimination of some candidate vaccines or by advancing others to efficacy trials.

The use of these models is not new; they have played a role in the development of some of the vaccines in use today. However, popularity has increased in recent year, in particular in relation to the assessment of vaccines (Darton et al., 2015). Several CHIM studies using different infectious pathogens have been reported in the literature, but very few in LMIC settings. Exceptions include a malaria infection model that has been successfully conducted in Kenya (Hodgson et al., 2015) and a

Shigella sonnei CHIM study in Thailand, which was the first of its kind in an endemic region (Bodhidatta et al., 2012). Recently, a global research funder has committed to the expansion of the models to ensure that vaccines are relevant to the people most at risk in endemic regions, recognising the need for community and political engagement as well as clear ethical and regulatory frameworks (Wellcome, 2017).

Example of a CHIM study: ‘Shigella sonnei human challenge model in Thailand’ Bodhidatta et al., 2012

Three groups of 12 healthy adult volunteers were orally challenged with two different concentrations of *Shigella sonnei* strain 53G as part of a dose escalating inpatient trial. The primary purpose of this study was to identify the dose of *S. sonnei* 53G required to elicit clinical disease in at least 70% of Thai adult subjects. While the paper did not focus on ethics, the authors concluded that to ensure that populations with *Shigella* disease burden benefit from vaccination, vaccine efficacy testing should be conducted using populations where *Shigella* is endemic. This may ensure that safe and effective doses of vaccines are used in these populations, which might be quite different from doses used in more naïve populations.

5.1 Ethical issues in CHIMs

Scientific rationale: CHIMs raise ethical issues about the scientific justification for using such a model – which generally must be avoided if the anticipated scientific knowledge could be generated from animal research (Darton et al., 2015; Miller & Grady, 2001).

Risk/benefit to participants: By their very nature – i.e., deliberately exposing a healthy person to an infectious pathogen – CHIMs raise a key ethical question: are these experiments (ethically) permissible at all? If they can be done, how much risk may participants be exposed to? So the main concern here is about risk of harm to participants (Hope & McMillan, 2004). Also, with such studies, there should be appropriate facilities to monitor and manage the symptoms and infection caused by the CHIM (Miller & Grady, 2001). A further ethical concern is the risk to the community. In particular, there is the question of establishing the appropriate time after infection for trial participants to re-join the community in order that they do not pose risk to other community members.

Vulnerability and community consultation: Furthermore, because the idea of deliberately injecting participants with a pathogen that can make them sick might be sound very strange and cause distrust of the research enterprise, there is need for meaningful community engagement with key stakeholders to facilitate better understanding, trust and acceptance of CHIMs (Hodgson et al., 2015).

Informed consent: The informed consent process in CHIM studies must ensure that participants understand that their participation involves being deliberately infected with a disease-causing organism and that this will make them ill and experience some acute disease symptoms. Investigators must disclose all the known potential risks of participating in CHIM study so that potential participants can understand and make informed decision regarding participation (Bambery et al., 2016). A question remains, however, as to how informed consent relates to research risk. Can a well-informed participant consent to any amount of risk if the social value of the study is high enough?

Compensation: CHIM studies raises an important and long-standing ethical issue regarding offering appropriate payments to participants. Careful consideration needs to be given to the level of financial compensation given to participants in order to avoid potential undue inducement and blinding to the potential risks or harms of participation (Miller & Grady, 2001).

6. Current guidelines on alternative trial designs

While there is a growing volume of literature on alternative clinical designs, the ethical issues associated with such issues have not been adequately addressed in existing research ethics guidelines. Table 1 summarizes the key issues addressed by guidelines.

The recently revised Council for International Organisations of Medical Sciences (2016) guidelines for health-related research involving humans provide a strong steer on the use of alternative designs in the context of research in disaster and disease outbreak:

‘In clinical trials, the randomised-controlled trial design is often considered the “gold standard” for collecting robust data. However, researchers, sponsors, research ethics committees and others must explore alternative trial designs that may increase trial efficiency and access to promising experimental interventions while still maintaining scientific validity. The methodological and ethical merits of alternative trial designs must be carefully assessed before these designs are used. For example, when testing experimental treatments or vaccines during an epidemic, the appropriate trial design will depend on the promise of the investigational agent, a variation in critical background factors (for example mortality and infection rates), and measurement of outcomes, among others. Researchers and sponsors must carefully evaluate the relative merits of different designs (for example observational or placebo-controlled) based on these factors.’ (p77)

Table 1

| Type of design | Existing guidance | Key ethical aspects covered |
|-------------------------|---|---|
| Adaptive trials | Food and Drug Administration (2010) https://www.fda.gov/downloads/drugs/guidances/ucm201790.pdf | <ul style="list-style-type: none"> ▪ Safety concerns for patients in certain adaptive designs e.g. dose-escalation studies ▪ Statistical considerations e.g. control of Type 1 error rate ▪ Operational concerns e.g. complexity of adaptive designs , difficult interpretation of results |
| | European Medicines Agency (2007) http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003617.pdf | <ul style="list-style-type: none"> ▪ Methodological aspects of adaptive trials e.g. confidentiality of interim results and potential bias |
| Controlled human | Academy of Medical Sciences (2005) https://acmedsci.ac.uk/file-download/34796-Microbia.pdf | <ul style="list-style-type: none"> ▪ Scientific and social value of proposed research ▪ Informed consent ▪ Recruitment and undue inducements or coercion ▪ Fair inclusion/exclusion of participants ▪ Risk of harm ▪ Safety monitoring |

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| infection models | WHO (2016) http://www.who.int/biologicals/expert_commi_ttee/Human_challenge_Trials_IK_final.pdf?ua=1 | <ul style="list-style-type: none"> ▪ Risks/benefits to research participants and society ▪ Informed consent ▪ Vulnerable populations with diminished capacity to consent ▪ Need for independent ethics review |
| Cluster randomized trials (including Stepped Wedge Design as a form of CRT) | CIOMS 2016 (p 79) http://cioms.ch/ethical-guidelines-2016/WEB-CIOMS-EthicalGuidelines.pdf | <ul style="list-style-type: none"> ▪ Who are the research participants and what other individuals or groups are affected? ▪ Informed consent process ▪ Ethical acceptability of a no-treatment control arm? ▪ Role of gatekeeper permissions |
| | DHHS (2014). https://www.hhs.gov/ohrp/sachrp-committee/recommendations/2014-july-3-letter-attachment-c/index.html | <ul style="list-style-type: none"> ▪ Scientific validity ▪ Who is the research participant? ▪ Identifying the risks and benefits of the research ▪ Informed consent process ▪ Role of gatekeeper permissions |
| | Ottawa statement on the Ethical Design and Conduct of CRTs (2012) http://journals.plos.org/plosmedicine/article/file?id=10.1371/journal.pmed.1001346&type=printable | <ul style="list-style-type: none"> ▪ Justification of CRT ▪ Need for independent ethics review ▪ Identifying who is the research participant ▪ Obtaining informed consent, ▪ Role of gatekeepers in protecting group interests ▪ Risk/ benefits assessment ▪ Protection of vulnerable participants |

Annex 2 Key References

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