



**Global Forum on
Bioethics in Research**

Conference booklet:

***Ethics of alternative clinical trial designs and methods
in LMIC research***

Bangkok, Thailand

28 and 29 November 2017



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Introduction

Welcome to the Global Forum on Bioethics in Research (GFBR) meeting on the “*Ethics of alternative clinical trial designs and methods in low- and middle- income country research*”.

Alternative clinical trial designs and methods are increasingly being used in place of the conventional randomised controlled clinical trial (RCT) in low- and middle- income countries (LMICs). These approaches – including adaptive, cluster randomised and stepped wedge designs and controlled human infection models – offer a number of 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.

The theme of this meeting provides an exciting opportunity to build on the Forum’s legacy as a global platform for debate on ethical issues in international health research. Specifically, the meeting will address the pressing need for the global bioethics and research community and regulators to find mutual ground for discussion and a shared understanding of the challenges and opportunities presented by these alternative approaches; only then will their full potential to address the health needs in LMICs be realised. We are very pleased to have participants from 35 countries (see map of participants’ countries) and a range of disciplines and look forward to a meeting where the GFBR can help promote open global dialogue on the ethical issues related to alternative clinical trial designs and methods.

On behalf of the GFBR funders I would like to extend our thanks to our local host Mahidol Oxford Tropical Medicine Research Unit for their support in the preparation of the meeting and the warm welcome to Thailand. I would also like to thank the GFBR Steering Committee and, most especially, the Planning Committee of this meeting. I very much hope the meeting will be a positive experience for us all.

Katherine Littler, Wellcome

On behalf of the GFBR funders: Wellcome; the National Institutes of Health; the UK Medical Research Council; and the Bill & Melinda Gates Foundation



Members of the GFBR Steering Committee:

Anant Bhan, India;
 Phaik Yeong Cheah, Thailand;
 Katherine Littler, UK;
 Florencia Luna, Argentina;
 Paul Ndebele, Zimbabwe;
 Michael Parker, UK;
 Rachel Knowles, UK;
 Barbara Sina, USA;
 Ross Upshur, Canada;
 Teck Chuan Voo, Singapore;
 Douglas Wassenaar, South Africa;
 Carla Saenz, USA.

Members of the GFBR Planning Committee for this meeting:

Phaik Yeong Cheah, Thailand;
 Nicholas Day, Thailand;
 Rieke van der Graaf, Netherlands;
 Charles Weijer, Canada;
 Annette Rid, UK;
 Katherine Littler, UK;
 Patricia Njuguna, Kenya;
 Patricia Saidón, Argentina;
 Ross Upshur, Canada.

Map credit: The Pixel/Shutterstock.com

Background to the GFBR

Background

The GFBR is an informal partnership established by a number of organizations with a shared interest in the ethics of conducting research involving people in low- and middle-income countries. The Forum meets annually, with an emphasis on discussion and the development of networks.

Meetings began in Bethesda, USA in 1999 and subsequently convened in: Bangkok, Thailand in 2000; Cape Town, South Africa in 2002; Brasilia, Brazil in 2002; Paris, France in 2004; Blantyre, Malawi in 2005; Karachi, Pakistan in 2006; Vilnius, Lithuania in 2007; and Auckland, New Zealand in 2008.

Following a period to reflect on the structure and funding of the Forum between 2009-13, the GFBR was re-launched at a satellite meeting of the International Association of Bioethics in Mexico City, Mexico in June 2014. It renewed its emphasis on providing a platform for individuals from low- and middle-income countries to bring forward ethical issues affecting their research practice for dialogue and discussion. The first full meeting took place in Annecy, France in 2015 on the theme ‘emerging epidemic infections and experimental treatments’ and the GFBR fellowships scheme was launched that year (see page 97). The second meeting took place in Buenos Aires, Argentina in 2016 on the theme ‘the ethics of research in pregnancy’.

The GFBR aims to provide a global platform to bring together key stakeholders from different geographical, cultural and scientific communities to debate the ethics, legal and public policy issues relating to international health research.

The key values of the GFBR are to:

- promote ethically conducted research;
- global development for health research ethics, particularly in low- and middle-income countries; and
- facilitate partnerships between the global north and south.

GFBR meetings aim to:

- maintain and strengthen the protection of human participants in health research;
- provide a forum for low- and middle-income country perspectives on ethical issues in research;
- explore opportunities to enhance capacity for the ethical review of research;
- create a context for scientists, ethicists, community representatives, policy-makers, industry and other relevant stakeholders to collaborate and talk in an environment of mutual cooperation and respect.

These aims are kept under review and refined by the Steering Committee.

Agenda

Monday 27 November 2017

17:00-19:00 | *Registration*

18:30-19:30 | **Planning Committee meeting (Room: Epsilon)**

Tuesday 28 November 2017

08:00 | *Registration*

08:30 | **Welcome and introduction**
Nick Day and Phaik Yeong Cheah, Mahidol Oxford Tropical Medicine Research Unit, Thailand

08:45 | **Keynote presentation:** HIV vaccine efficacy trials and standard of care considerations
Glenda Gray, President and CEO, South African Medical Research Council

Theme 1 | **Cluster randomised trials**
Chair: Charles Weijer, Western University, Canada

09:15 | **Introduction to the theme**

09:25 | **Case Study 1:** Ethical issues of the PolyIran study: A cluster randomized trial nested within Golestan cohort study
Gholamreza Roshandel, Golestan Research Center of Gastroenterology and Hepatology, Iran

09:45 | **Case Study 2:** Lessons from an adaptive multi-arm multi-stage trial of strategies for improving linkage into HIV care or prevention in Malawi
Augustine Choko, Malawi-Liverpool Wellcome Trust Clinical Research Programme/
London School of Hygiene & Tropical Medicine, UK

10:05 | **Discussion**

10:25 | **Breakout group discussion**

11:00 | *Tea/coffee break*

Theme 2

Stepped wedge

Chair: Rieke van der Graaf, University Medical Centre Utrecht, Netherlands

11:30

Introduction to the theme

11:40

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)

Karla Hemming, University of Birmingham, UK and Guillermo Ambrosio, Epidemiological Research Centre in Sexual and Reproductive Health (CIESAR), Guatemalan Ministry of Public Health

12:00

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

12:20

Discussion

12:40

Breakout group discussion

13:15

Poster session

13:40

Lunch

Theme 3

Adaptive platforms

Chair: Ross Upshur, University of Toronto, Canada

14:30

Introduction to the theme

14:40

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

Scott Berry, Berry Consultants, USA

15:00

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

Srinivas Murthy, University of British Columbia, Canada

15:20

Discussion

15:40

Tea/coffee break

16:10

Breakout group discussion

16:45

Pecha Kucha

Chair: Barbara Sina, Fogarty International Centre, National Institutes of Health, USA

17:15

Photograph of participants and meeting close

18:00

Meet in the foyer for departure for dinner

Wednesday 29 November 2017

07:30 – 08:30	Steering Committee meeting (Room: Epsilon)
08:30	Summary – Key themes from day 1 Teck Chuan Voo, National University of Singapore, Singapore Anant Bhan, Yenepoya Medical College, India
Theme 4	Controlled human infection models Chair: Nick Day, Mahidol Oxford Tropical Medicine Research Unit, Thailand
09:00	Introduction to the theme
09:10	Case Study 7: Control of invasive Salmonella in Africa and Asia – Is there a role for establishing controlled human infection models in endemic countries? Meriel Raymond, Oxford University, UK
09:30	Case Study 8: Experiences and perceptions of study participants in a malaria challenge study in Kilifi, Kenya Dorcas Kamuya, KEMRI-Wellcome Trust Research Programme, Kenya
09:50	Case study 9: The case of Zika virus human challenge studies Ricardo Palacios Gomez, Butantan Institute, Brazil
10:10	Discussion
10:30	Breakout group discussion
11:00	<i>Tea/coffee break</i>
Theme 5	Current guidance and regulation: Regional perspectives Chair: Mike Parker, Oxford University, UK
11:30	Introduction to the theme
11:40	Presentation: Current international ethical guidance and regulations on use of alternative research designs Rieke van der Graaf, University Medical Centre Utrecht, Netherlands Presentation: CHIMS: What does it mean to be a responsible research funder? Katherine Littler, Wellcome, UK Response from different regional perspectives and open discussion: East Africa - Claude Kirimuhuzya, Kampala International University, Uganda Caribbean - Derrick Aarons, Caribbean Public Health Agency, Trinidad and Tobago Latin America - Carla Saenz, Pan American Health Organisation, USA Southeast Asia - Cristina Torres, Forum for Ethical Review Committees in the Asian and Western Pacific Region, Philippines
12:40	Poster session
13:00	<i>Lunch</i>

Theme 6

Current guidance and regulation: Gaps and creative solutions

Chair: Katherine Littler, Wellcome, UK

14:00

Introduction to the theme

14:05

Presentation: Informing ethical evaluations of adaptive clinical trials through simulation
Roger Lewis, University of California, USA

Panel and open discussion: How well does the current guidance, regulation and tools address the need? What gaps remain and can we identify creative solutions?

Rieke van der Graaf, University Medical Centre Utrecht, Netherlands

Roger Lewis, University of California, USA

Phaik Yeong Cheah, Mahidol Oxford Tropical Medicine Research Unit, Thailand

Charles Weijer, Western University, Canada

Patricia Saidon, Instituto de Investigación en Salud Pública Argentina

15:00

Tea/coffee break

15:30

Key themes panel

Chair: Glenda Gray, South African Medical Research Council

Panellists:

Paul Ndebele, Medical Research Council, Zimbabwe

Anant Bhan, Yenepoya Medical College, India

Carla Saenz, Pan American Health Organisation, USA

Rachel Knowles, Medical Research Council, UK

Mike Parker, Oxford University, UK

16:45

Conclusions, presentation of poster award and GFBR award

Chairs: Paul Ndebele, Medical Research Council, Zimbabwe and Anant Bhan, Yenepoya Medical College, India

17:00

Meeting close

Case Studies

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

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Reza Malekzadeh, Digestive Diseases Research Institute, Tehran University of Medical Sciences, Tehran, Iran

Brief description of the research project

Coronary artery disease mortality is anticipated to increase twofold from 1990 to 2020, and 82% of the increase will occur in low- and middle-income countries.^{1,2} The polypill concept, a fixed dose combination pill of established generic drugs, may simplify the treatment regimen, reducing the cost whilst preventing up to 88% of heart attacks and 80% of strokes.³ We designed the PolyIran study to assess the effectiveness and safety of polypill tablet (aspirin, atorvastatin, hydrochlorothiazide and either enalapril or valsartan) for primary and secondary prevention of cardiovascular diseases.^{4,5}

This is a cluster-randomized trial nested within Golestan cohort study (GCS). The trial participants were randomly allocated, in clusters, to receive a package of non-pharmacological preventive interventions either alone (minimal care arm) or together with a once daily polypill tablet (polypill arm). An additional comparison will be made between these two arms and the remaining GCS participants who lived in rural areas, were aged 50 years and over and were not selected to participate in the main trial. The usual care arm receives neither minimal care from the PolyIran study team nor polypill but they receive usual care as currently provided by the public and private sectors.⁴

The primary outcome is the occurrence of major cardiovascular events within five years of enrolment. These outcomes include either hospitalization for acute coronary syndrome (non-fatal myocardial infarction and unstable angina), fatal myocardial infarction, sudden death, heart failure, coronary artery revascularization procedures, non-fatal and fatal stroke. Outcomes are ascertained by the GCS follow-up team using multiple methods including annual telephone contact, home visits, interview, and reviewing medical documents. Personnel in charge of outcome ascertainment act independently of the PolyIran trial team and are blinded to allocation arm of the PolyIran trial.⁴

Background

The study makes use of the infrastructure of the GCS study and the established rural primary health care system and addresses the value of the polypill in a real life setting. The GCS study was launched in January 2004 to investigate the epidemiology of oesophageal cancer in participants 40–75 years old in Golestan province, Iran. It includes 50,045 participants, 20% enrolled from Gonbad city and 80% from rural areas: the villages in the regions of Gonbad, Aq-Qala and Kalaleh.⁶ GCS participants who lived in rural areas and were aged 50 years and over at the beginning of the trial constituted the sampling frame for the PolyIran study. From this sampling frame, individuals were selected using a simple stratified random selection procedure in proportion to the number of eligible inhabitants in each village. These random samples from each village constituted the clusters. Accordingly, all participants within a cluster were randomized to receive the intervention or control conditions.

Ethical issues

1. **Justification for using cluster randomization**
2. **Obtaining informed consent**
3. **Dealing with current clinical practice in the study population**
4. **Post-trial provisions**

Commentary

1. Justification for using cluster randomization: In this population, residents of the villages have close familial relationships and it is a common behavior to share medicines among residents. Therefore, the issue of contamination due to sharing of medicines was a major concern in this study. We consider cluster randomization to avoid of this contamination(4). Cluster randomization at the level of villages minimizes the risk of contamination through pill sharing.

2. Obtaining informed consent: Although the PolyIran trial is a cluster randomized trial, the interventions of interest (polypill tablet and minimal care) are delivered to subjects individually. Accordingly, written informed consent was obtained from each subject. The subjects were aware that they may be allocated to the polypill arm (intervention) or the minimal care arm (control). The majority of GCS participants (about 80%) were illiterate and obtaining informed consent therefore raised many obstacles. Dedicated local (native) interviewers were trained and assigned to obtain informed consent. Interviewers were trained to provide all information (according to informed consent) to participants and to make sure that all information was comprehensive and clear to participants.

There was a challenging point regarding informed consent for the usual care arm. The usual care arm consisted of the remaining GCS subjects who were not selected to participate in the main trial. In fact, they had not been invited to PolyIran study site for recruitment. These GCS subjects had already consented to provide observational data at the outset of GCS. But, the informed consent obtained during the enrollment phase of the GCS was not sufficiently broad to permit investigators to use collected data on cardiovascular diseases for PolyIran project. Therefore, the issue was mentioned in the protocol of the PolyIran study and the protocol was reviewed by the IRB of the Tehran University of Medical Sciences. The IRB approved that there was no need for new informed consent for using available data on cardiovascular outcomes in these subjects.

3. Dealing with current clinical practice in the study population: Some of the PolyIran subjects (in both arms) suffered from CVD before recruitment. These subjects had already been referred to a specialist physician in study area and were under treatment using different medications. In these cases, for control arm participants, we just recorded their medications and recommended them to continue the medications according to their physician's advice. But, for intervention participants, we sent a letter to patients' physician, explaining the study plan and the combination of polypill tablet to the physician and asked the physician (if it is applicable) to adjust the participants' medication according to polypill components. In these cases, all medications and physicians' orders were recorded for future follow-up and analysis.

4. Post-trial provisions: Post-trial provision is a major ethical issue in this study. If the polypill is shown to be safe and effective, it will be provided to all study subjects, including those in the minimal care arm, after termination of the project. But, for how long should we continue providing the polypill tablet to subjects? Naturally, there are concerns regarding feasibility of this decision for long-term access.

The other issue is should usual care arm subjects be provided with the polypill? The usual care arm consisted of the remaining GCS subjects who were not selected for either of the polypill or minimal care arm. In fact, they were not invited to PolyIran study site for recruitment. Therefore, it has been decided not to provide polypill tablet to these subjects after termination of the project.

The issues regarding post-trial provisions remains open and, as we approach the end of the study, we anticipate the need for more detailed discussions.

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

Augustine T Choko, Malawi-Liverpool Wellcome Trust Clinical Research Programme, Blantyre, Malawi/
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Charles Weijer, Rotman Institute of Philosophy, Western University

Katherine Fielding, Department of Infectious Disease Epidemiology, London School of Hygiene and Tropical
Medicine, London, UK

Brief description of the research project

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 (ISRCTN18421340). 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) conditional on linkage after self-testing with one arm testing phone call reminders. The trial randomised 36 ANC days (clusters) in the first stage in which 1007 (93%) of 1084 eligible women were recruited between August and November 2016. An independent set of 35 ANC days were randomised for the second stage with 97% (1236/1275) women recruited between January and May 2017. The primary outcome was the proportion of male partners who tested for HIV and linked to clinic for HIV treatment or prevention within 28 days. The main outcome measurement was by counting the number of male letters presented at the clinic. Tablets were used to collect data from women and men. We highlight some ethical challenges encountered in this trial.

Background

There are about 1.1 million deaths due to HIV infection worldwide with an estimated 1.9 million people becoming infected every year, the majority in low and middle income countries (LMIC).¹ However, only 60% of people living with HIV are aware of their HIV status, whilst only 46% of those who know their status have started antiretroviral therapy.¹ The benefits of timely initiation of antiretroviral therapy² and effective HIV prevention including voluntary medical male circumcision³⁻⁶ have changed the emphasis of HIV testing services from learning one's status to appropriate linkage and retention.¹ However, uptake of HIV testing services and linkage into care or prevention remains below current targets⁷ in most LMICs.⁸ Recent targets aim to diagnose 90% of all people living with HIV (PLWH), 90% of those diagnosed should start HIV treatment, and 90% of those starting treatment should be virally suppressed.⁹ However, only 48% of newly diagnosed HIV positive people link to HIV care let alone access HIV prevention methods such as voluntary medical male circumcision globally.¹⁰ Of more concern has been the finding that whilst HIV incidence decreased before 2010, it has remained static since then.¹¹

Major barriers to HIV testing include lack of confidentiality, direct and indirect costs incurred by users, and lack of perceived benefits to accessing HIV testing services.¹²⁻¹⁶ We thus designed the PASTAL trial to investigate the effect of interventions building on the successes of HIV self-testing^{17,18} in other populations targeting a hard to reach group of male partners.

Ethical issues

1. **Was the use of an adaptive cluster randomized design justified?**
2. **How was informed consent handled given that the unit of randomization was the ANC day?**
3. **Having conducted an interim analysis which showed that the standard of care was suboptimal, was there equipoise to justify continuation to the second stage of data collection?**
4. **How could the interventions be widely implemented post trial?**

Commentary

1. Was the use of an adaptive cluster randomized design justified? The interventions (letters, self-test kits and financial incentives) could only be best delivered in a group and not individually.¹⁹ Perhaps a better choice of cluster would have been the whole clinic as opposed to the ANC day as this would have more effectively prevented contamination. Randomisation of the entire facility to one arm would have eliminated presentation to the same clinic for different interventions thereby promoting fairness. For instance, a man who was in the standard of care arm waited for the trial HIV counsellor together with a man who was in a \$10 incentive arm. The two men shared information about the study leading to confusion for the man in the non-incentive arm as to what he was supposed to get at the end of his clinic attendance.

We found the adaptive design very *efficient* in this first ever multi-arm multi-stage cluster randomized trial. The efficiency was evident in the rapid recruitment of participants (each stage ~3 months) and the smaller sample size (~1100 participants per stage) for six trial arms.

2. How was informed consent handled given that the unit of randomization was the ANC day? On each day of recruitment, trial staff gave general information about the trial (no mention of differing arms) to women in a group. Then, women completed their ANC service before meeting one-on-one with a trial staff member who screened them for eligibility and completed informed consent process. Note that individual consent was feasible because of the small number of patients in each cluster (max. 75).

Additionally, recruitment of men through their pregnant partners meant that it was impossible to obtain written consent from the male partner despite being the target population. Therefore, a waiver of informed consent process was sought and granted by the institutional review boards. This approach compromises the rule of autonomy when it came to the man's decision to participate in the study. Indeed this may be a source of conflict among couples particularly in Africa where the prevalence of intimate partner violence is high.²⁰

3. Having conducted an interim analysis which showed that the standard of care was suboptimal, was there equipoise to justify continuation to the second stage of data collection? The original sample size calculation assumed that the standard of care arm would have efficacy of 25% on the primary outcome from a previous trial.²¹ At interim analysis (end of stage 1), efficacy was 13% in this arm. This sparked debate during the trial data safety and monitoring board as to whether such a low efficacy standard of care should be carried forward to the second stage. The final decision was to maintain the standard of care in its original form because the pre-specified criteria for dropping arms did not include consideration to drop the standard of care.

The need to maintain a standard of care regardless of what is learned from the first stage in a multi-stage design is problematic. By definition, adaptive designs are meant to use the accumulating evidence to alter aspects of the trial²² hence continuing with a SOC arm which has less than the assumed efficacy may defeat the purpose of an adaptive trial design.

4. How could the interventions trialed here be widely implemented post trial? In the past ten years, there has been very strong interest to use behavioural economics interventions such as financial incentives to improve HIV outcomes.²³ Our trial aimed to identify candidate interventions for improving HIV testing and linkage for additional services for men including financial incentives followed by a Phase III study to confirm the findings.²⁴ We found that only the two fixed financial incentive interventions of \$3 and \$10 improved the primary outcome. However, policy makers remain unwilling to scale up or pilot within their programs despite the strong evidence in favour of these interventions. This begs the question of sustainability or indeed whether there is social value in conducting trials with these types of interventions.

Conclusions

In this novel adaptive cluster randomized trial, we noted ethical challenges with regards to the choice of a cluster, informed consent, potential lack of equipoise, and post-trial access to interventions. The application of an adaptive trial design to address a public health question was feasible and efficient.

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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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Brief description of the research project

"**¡Que Vivan las Madres!**" (QVLM) or "long-live mothers" is a Stepped-Wedge Cluster Randomised Trial (SW-CRT) that was conducted between January 2014 to January 2017 by the Epidemiological Research Centre in Sexual and Reproductive Health (CIESAR) in Guatemala. The aim of the study was 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.

During the study, 33 health centres from 6 regions in 2 districts Guatemala were sequentially randomised to initiate a package of three interventions, one of which was the PRONTO intervention.¹ The PRONTO intervention is a culturally-adapted training curriculum targeted at health care providers and traditional birth attendants. Other components of the intervention include media campaigns and training of traditional birth attendants. Extensive data collection procedures were established throughout the districts participating in the study.

The study found that the number of women giving birth in a health centre increased throughout the study period. Of those mothers giving birth in a health centre maternal mortality was low throughout, but the number of perinatal deaths decreased substantially. This finding of a decrease in perinatal mortality could be directly attributable to the intervention – given the randomised evaluation. Mother morbidity and perinatal morbidity also decreased after intervention was rolled out.

Background

The neonatal mortality rate in Guatemala is around 22 per 1,000 pregnancies²; and in the two rural districts where the study was conducted, the rate is double the national figure. In rural areas around 75% of mothers give birth at home and this is believed to contribute to the high neonatal mortality rate. Mothers are often reluctant to give birth in health centres as there is a strong sense that the traditional birth attendant is integral to maternal care. It is hoped that by encouraging more women to give birth in a health care centre, particularly when there are early signals that the birth is not going well, well help reduce the high neonatal mortality.

Furthermore, when mothers do give birth in a health centre, they often arrive late in the birth process, and the health care centres are poorly equipped to deal with complex births. The PRONTO intervention has been developed to tackle exactly this issue and has already demonstrated promising results and importantly fully engages the traditional birth attendant.^{1,3} In essence the PRONTO intervention uses reflective observation and feedback on simulated complex birth scenarios, to allow health care professionals and traditional birth attendants to consider how they can best equip their centres and staff to address these complex issues, all within the resource constraints of the particular health care centre.

The “**¡Que Vivan las Madres!**” study is a randomised stepped-wedge and cluster evaluation of this package of interventions. Evaluation of interventions in conjunction with their roll-out is possible with novel stepped-wedge designs, which randomly allocate clusters (e.g., communities or hospitals) sequentially to the intervention until all clusters are exposed.⁴ This stepped-wedge evaluation entails roll-out of this package of interventions, region by region, in a randomised order, until ultimately all regions have been exposed to the package of interventions.

Ethical issues

The SW-CRT is seeing an increasing amount of interest, with the number of published studies growing year-on-year.^{5,6} Reporting of key ethical protections in these studies, including research ethics review and informed consent, are inadequate.⁷ This is perhaps in part because these studies are often not classified as research.

The *Ottawa Statement on the Ethical Design and Conduct of Cluster Randomized Trials* provides ethical guidance for the conduct of cluster randomised trials, but it neither provides guidance specific to SW-CRTs neither does it provide guidance specific to LMICs.⁸ Furthermore, whilst academically this guidance is widely accepted, its principles are infrequently implemented in practice. This means there is a real danger that funders will commission SW-CRTs, whilst researchers lack guidance from whom informed choice about study participation should be obtained (and for what) and when research ethics committee review is required. This will tend to undermine the potential for *social benefit* when studies are not conducted with due consideration to potential biases (more likely when research studies misclassify individuals as research participants and cannot obtain consent due to logistical difficulties) and violate *ethical protections* for individuals participating (which is more likely the case when research studies are misclassified as non-research). Furthermore, a growing number of these studies are being conducted in emerging and developing economies.⁷

The *Ottawa Statement* suggests that health professionals targeted by a knowledge translation intervention are not research participants.⁸ Further, it states that patients are only research participants if they otherwise intervened upon or their identifiable private information is collected for study purposes. The *Ottawa Statement* also make clear that a waiver of consent is justified only when requiring informed consent would render the study infeasible and when the risks of participation are minimal.

Commentary

Two underlying principles of good research practice are quality study design and appropriate ethical consideration given to those who participate in research. Both principles must be fulfilled if research is to benefit the health of future populations whilst not compromising the rights and welfare of research participants. This case study will be used to generate discussion on a number of ethical issues raised by SW-CRTs.

1. To what extent was the conducted study research? SW-CRTs are an opportunity to provide a rigorous evaluation of interventions destined to be rolled-out on the basis of limited evidence. Research studies require research ethics committee review and approvals as well as trial registration; service evaluation generally does not. So in “**¡Que Vivan las Madres!**” should ethical committee review be obtained and should the study have been registered as a clinical trial? Was this study research; or should it be subsumed under the umbrella of service evaluation?

2. Was it justifiable to delay the roll-out of the intervention that had promising effectiveness? SW-CRTs are commonly used where there is a strong sense that the intervention will work. So, researchers’ need to justify the delay in providing a known effective or potentially effective intervention. So in “**¡Que Vivan las Madres!**” whilst all districts eventually received the PRONTO intervention, many mothers did not. Arguably, those mothers have been denied the potential benefits of the PRONTO intervention. Was this delay consistent with clinical equipoise?

3. Who were the research participants in this study? SW-CRTs often evaluate cluster-level interventions and just who are research participants may not be obvious. The *Ottawa Statement* elucidated some of these issues for parallel cluster trials. Yet, implications might be different in SW-CRTs in LMICs. Furthermore, while the identification of the research participant in cluster trials is known not to be straight forward, health care providers are rarely identified as the research participants. In “**¡Que Vivan las Madres!**” should the health care providers and the traditional birth attendants have been considered research participants? If so, what follows from this? Should health care participants and the traditional birth attendants be free to refuse the training? And is their informed consent required?

4. What other broader issues of consent in this trial? The *Ottawa Statement* recommends that researchers “get consent where possible” in cluster trials, and this commonly means obtaining consent for some study procedures (such as for data collected) but not others (such as exposure to the intervention). Further, it argues that a waiver of consent is commonly appropriate for cluster-level interventions. In “**¡Que Vivan las Madres!**” should consent have been sought for differing components of the trial (such as for example, use of their data)? If both health providers and women in labour are research participants, to what should each group have consented? Is the use a waiver of consent appropriate in this SW CRT and, if so, why?

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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)

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Brief description of research project

ATMIYATA intervention involves a two-tier community led mental health model that develops capacity of community volunteers (*Atmiyata Champions & Mitras*) to identify and provide basic, low intensity counselling to persons with common mental disorders (CMD). The intervention employs use of films based on social issues like domestic violence leading to mental health issues to raise community awareness.¹ We will employ a stepped wedge cluster randomised trial, using a repeated sampling designed to answer crucial questions of how effective the *Atmiyata* intervention is in reducing symptoms associated with CMD when implemented at scale. In this design, all clusters start at baseline in the control condition and each group of clusters are exposed to the intervention at regular intervals (the “steps”).² Data collection continues throughout the study, so that each cluster contributes observations under both control and intervention. It is a pragmatic study design, giving great potential for robust scientific evaluation.² Sample size for SW-CRT has been calculated to detect difference in CMD cases in intervention and control groups at 3-month follow-up. Sample size for the present study is calculated to detect 13 % difference in CMD cases at follow-up between intervention group (58% improved) and control (45% improved). The sample size is calculated using “stepped wedge” function of STATA 14. The number of steps (t)=4, number of clusters randomized per step (k)=14, average cluster size (m) of 4, intra-cluster correlation coefficient of 0.1 and alpha of 0.05 provide 80% power to the study. A total of 1,120 CMD cases will be enrolled in the study across the intervention and control group.

Background – relevant facts about the host country/community and disease studied

The study is based in rural parts of Mehsana district in state of Gujarat, India. Mehsana has a rural population of approximately 1.5 million (of which approximately 1 million are above 18 years of age). The district is divided into 10 blocks/ sub districts with 645 villages and 316,536 rural households (Census, 2011). Almost half (45.4%) of Mehsana’s rural population has a low standard of living as per the Standard of Living Index (SLI). The majority of residents (53%) are employed in agriculture. The strain on farming families is evident with uncertain climate change and its impact on small and marginal farmers. The community has well demarcated caste system in each village.

Mental ill health is a substantial public health burden in India. Approximately 70 million people in India experience some form of mental illness, of which many have limited to no access to mental health support and treatment.³⁻⁷ Of those experiencing mental health problems, approximately 20% of the Indian population is affected by common mental health disorders (CMDs), such as anxiety and depression. Disorders such as these are often under-detected and undertreated due to a variety of factors.⁸ People with mental health problems often face discrimination in their communities⁹⁻¹³, which can reduce willingness to seek help from mental health care providers. Supply side factors, such as the paucity of trained mental health professionals in India, means that there are insufficient human resources to address the burden of CMD in the community¹⁴, particularly in rural areas¹⁵.

Ethical issues and commentary

For large scale public health research, a cross over unidirectional Step Wedged Cluster Randomised Trial is a better alternative to a conventional RCT from a logistic, social and political view point.¹⁶ Logistically, rolling out a large scale public health intervention at one point is not possible and from community viewpoint SW CRT is more acceptable as everyone will get an intervention at the end of trial. Sometimes politically it becomes mandatory to start the intervention from specified geographical area due to political pressure, and SWCRT allows the same.¹⁶ SWCRT allows implementation to get more refined at each step and learn as you go.¹⁷

SWCRT is subject to the same foundational ethical principles as all clinical research: respect for persons, beneficence, justice, and respect for communities.¹⁷ We are facing the following ethics issues or challenges:

1. Gatekeeper permission - In our case study one cohort represents 140 to 150 villages. At every village level, our selected volunteers are doing public awareness activities via films based on issues like domestic violence, unemployment and addiction. We are taking permission from the village head or from community leaders like religious leaders or influential community members from every village where researcher collects data for CRT. The permission is largely to approach the members of that village.

The definition of a gate keeper has been given in Ottawa statement for ethical guidelines on conduct of CRT and previous work done by Weijer et al.^{17,18} In our CRT the challenge is to specify formal gatekeeper as per the definition. So we took permission from a village head which is a sub unit of the cluster. Are we allowed to deviate from standard definition of the gatekeeper and take the permission from someone else in the cohort? Also, there is unclarity about gatekeeper permission need to be obtained verbally or in writing.

2. Cluster Randomization process - In our study we have four clusters divided geographically with each containing 120 to 130 villages, and 14 Primary health centers in each cluster. This geographical division helps in less contamination. In theory, we switch clusters “at random”, but researchers often made arrangements which cluster can go first for logistical reasons.¹⁷ In our case study we started with the first cluster. The decision of selecting this cluster was partly due to administrative and political reasons. During one of the district level meeting it was suggested that we should start our implementation from a specified block in the district. This suggestion came from health officials and a politician.

3. Principle of clinical equipoise and treatment in control area - The principle of clinical equipoise is one of the most fundamental ethical principles for justifying randomised controlled trials.¹⁹ The Atmiyata intervention is about counselling people with distress via trained community volunteers. The counselling techniques which have been used are evidence based and used by lay health counsellors. We are trying to test effectiveness of these methods of counselling at large scale with trained volunteers. We are using SWCRT for this large-scale community intervention. In a sense this may break the principle of equipoise. So withholding people in the control area from a proven effective intervention is not fair, and not implementing the intervention at all means we withhold even more people from the intervention. This poses an ethical challenge for us. Also in case of large implementation trials, we need to have a protocol for care principles in the control area. Because in low-middle income countries usual care means no care, so having an enhanced care protocol will help participants from the control area.

Conclusions

SW CRT is a preferred option in public health research for large scale implementation mainly due to logistic, social and political/policy perspective. SW CRT is an attractive design for researchers and its use in public health research is increasing. Various guidelines like Ottawa statement, UK Medical research council guidelines and work from Weijer and colleagues address ethical challenges in CRT. The ethical challenges we are facing in our study need to be discussed. It will be good to have a guidance and future guidelines on issues about gatekeeper, cluster randomisation and unfairness of treatment

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

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Description of the research project

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 IRB approval in Sierra Leone, but the trial was not initiated due to the waning of the epidemic. The trial remains ready to initiate if needed.

Background

The 2014-2015 Ebola epidemic in West Africa was one of the most challenging public health emergencies the global community has faced. Within the midst of this public health emergency, multiple efforts were made to design, initiate, and conduct clinical trials to evaluate promising vaccination and therapeutic strategies for Ebola. As noted in a recent report from the National Academy of Medicine and others, there are very few solid conclusions that can be drawn from these research efforts. Research efforts were hampered by multiple challenges, including a lack of coordination of research efforts, local concerns regarding the motivations for and safety of investigational treatments, a failure to engage local communities, and concerns regarding the appropriateness of randomization in the setting of a highly lethal epidemic.

During the epidemic, the Bill and Melinda Gates Foundation supported the design and implementation of an adaptive platform clinical trial that was designed with the potential to investigate multiple therapies simultaneously, singly and in combination, and incorporating 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 platform trial was poised to start with randomization to the following therapies as a function of the current accrual rates: an anti-viral, Sunitinib (a receptor tyrosine kinase inhibitor), Erlotinib (kinase inhibitor), Atorvastatin, Irbesartan (Angiotensin II AT1 Receptor Blocker), and Azithromycin (antibiotic).

Adaptive platform trials are relatively complex clinical trials designed to be able to evaluate multiple treatments simultaneously and are intended to continue beyond the evaluation of any one treatment, while maximizing statistical and clinical efficiency. Platform trials are either ongoing or being initiated in oncology, infectious diseases, pulmonary and critical care, neurology, and other areas. Such a trial has, to our knowledge, never been implemented in a low and middle-income country (LMIC) setting.

This trial design effort likely represents the most advanced application of innovative clinical trial design techniques in a LMIC setting, especially in response to a life-threatening epidemic.

The Ebola Platform trial was approved by Ethics Committees in both the United States and Sierra Leone and reviewed and supported by the U.S. Food and Drug Administration (FDA). Logistical issues including data management, drug supply, and initiation of local sites was also completed, although the trial was not initiated because of the resolution of the West African Ebola epidemic in 2015. However, the trial remains in place and could be activated rapidly should there be a substantial resurgence of Ebola in the area.

Ethical issues

Ethical issues that were considered in the design of the clinical trial and incorporated into the final design include:

1. The tradeoff between trial complexity, operational constraints, and trial efficiency. The more complex trial designs provided the ability to answer more questions efficiently and improve care for patients in the trial, but provided a higher burden to explain to review boards and patients. Specifically:

- How well would the platform trial design be understood by different research stakeholders in LMICs (e.g. investigators, research ethics committees [RECs], and regulatory authorities)? How could the characteristics of the trial best be explained to local RECs and regulatory authorities?
- How could investigators explain complex information regarding the adaptive trial design to a prospective participant?
- The ability for investigators to explain the adaptive platform trial design to local communities to assess acceptability.

2. The question of whether a standard-of-care (SOC) arm was ethically appropriate in the trial. We created a design that 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.

3. The platform trial has been demonstrated to provide better care for patients in the trial as well as provide more efficient answers – a strict dominance – how could we communicate this to the local healthcare providers, review boards, and scientific community?

Commentary and conclusions

- Adaptive platform trial designs hold out the prospect for improving the ethical balance of clinical trials conducted in LMICs; however, substantial work remains to ensure:
- We can answer larger ethical questions about the positioning of clinical trials in LMIC, e.g., whether multiple trials should be performed rather than a single integrated adaptive platform.
- Such trials are understood by the scientific community – there are misperceptions that adaptations do not improve scientific rigor and efficiency and thus they may present an ethical burden
- Such trials are only implemented in settings in which the advantages from ethical, scientific, and societal perspectives justify the additional complexity and implementation work;
- That, when the situation justifies the additional effort, innovative trial designs are utilized in LMICs to improve the ethical balance, scientific value, and public health benefits associated with the trials;
- That the important characteristics of platform trial designs are effectively communicated to local officials, ethics committees, healthcare providers, and prospective participants to both gain local engagement and to ensure meaningful consent is obtained from participants; and
- That logistical challenges associated with the implementation of innovative adaptive platform trials in LMICs are addressed, and practical solutions are identified and disseminated

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

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Background

A variety of treatment options are currently available for critically ill children with acute respiratory failure and infections. In many cases, clinicians lack data on the best management strategy. Difficulties in performing well-designed studies in this population include the time-sensitive nature of identifying and enrolling participants, and the distress involved with parental decision-making.^{1,2} For acutely ill children, alternate consent models, including deferred consent and waivers of consent have been employed to both expedite enrolment and to optimize difficult conversations with families during stressful periods.

Given the variety of possible interventions for critically ill children with infections, an adaptive comparative-effectiveness platform trial would be valuable. A platform trial tests a variety of interventions, focusing on a specific population rather than any one treatment, and examines which interventions produce the best outcome. Adaptive trials respond to data accumulated within the trial to modify their performance – for example, randomization may preferentially accrue to the arm performing better.

Adaptive platform trials for comparative-effectiveness evaluations serve a variety of needs in this context³: they address a high-risk, complex population and examine which treatments, out of many, are best, both sequentially and simultaneously; they have the ability to preferentially randomize children to the better performing arms, based on pre-existing data, thereby minimizing risks of harm; and they examine the role of already frequently administered therapies, possibly thereby qualifying for ‘minimal risk’ assignments.

This proposed trial, currently in the design phase, 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 are still under discussion, but will likely include fluid administration strategies, antibiotic duration, and amount of ventilation support.

Ethical issues

Consent

1. Platform trials will incorporate a number of interventions. Some may be of higher risk than others. For example, ventilator support strategies may be deemed more risky than fluid administration options. Can a one-time consent model be comprehensive enough to achieve the appropriate amount of participant information?
2. Given the complexities of adaptive trials, with response-adaptive randomization being a major feature, can fully informed consent be assured? Classic ‘randomization’ language used in traditional informed consent forms cannot be used; can the adaptive randomization concept be explained in a timely and clear manner?

Risks & Benefits

1. The possibility of harm implicit in randomizing is partially mitigated by adaptive randomization, where preferential randomization will be towards the group performing better in data thus far accumulated. Hence, the likelihood of consenting has been shown in simulations to be higher.⁴
2. If an ultimate goal is to increase the participation of vulnerable populations in clinical research, then adaptive trials may provide substantial benefit, compared to traditional randomization.
3. Comparative effectiveness studies directly compare existing healthcare interventions to evaluate the optimal management strategy. Assignment to any specific arm, therefore, should pose no more risk than usual care. Should platform-based comparative effectiveness research be considered a minimal risk study?

Provider-patient relationship

1. Platform-based research involves a number of interventions, tested simultaneously, where individual participants could, in theory be randomized to 3-5 separate interventions. This oftentimes takes decision-making autonomy from the treating clinician and shifts it to a research protocol, leading to possible decreased enthusiasm to participate.

Commentary

Consent

1. One proposal to overcome this is to use a tiered consent model, where participants can be enrolled in the platform through a waiver of consent, but if qualifying for a specific intervention deemed more than minimal risk, informed consent is sought. Another option is to use a dynamic consent model, where consent is sought and re-sought and research staff is frequently available for questions.⁵ In low-income settings, this will be logistically challenging, but the principle of having ongoing interaction between researchers and participants is vital.

2. Achieving fully informed consent for an adaptive trial in a time-sensitive manner is challenging. One option is to defer the explanation of complex aspects of trial design until the acute health crisis is resolved. The bulk of explanation can then occur after the initial fear and distress of having a severely ill child has been reduced. Through the use of infographics, videos, and explainer sheets, the adaptive concept has been shown to be explainable to adult participants who are not critically ill.⁴ Community engagement and pre-trial work with relevant stakeholders is crucial in ensuring that the principles of adaptive designs are clear and understandable, with piloting of consenting strategies with volunteers. Another option is to avoid explaining the randomization process altogether, and simply explain the study during the consent process and that the patient will be ‘assigned’ to a specific arm.

Risks & Benefits

1. Minimal risk studies, according to rules in various jurisdictions, are those where the probability or magnitude of harm for those who participate in research are no more than for those who do not participate. They imply a smaller burden on ethics boards during the review process and may be eligible for waivers of informed consent. For comparative-effectiveness research, the risks of the research relate primarily to data collection and privacy, and not to the risks of the intervention itself. However, on the contrary, these risks are not insignificant, especially with multi-jurisdictional studies with data sharing across borders.

Provider-patient relationship

1. This is an unexplored facet of platform trials. Given the possible benefits of adaptive platform trials as described, it can be argued that there is benefit in participating for both providers and patients. However, when many aspects of patient care are embedded within a research protocol, providers have voiced discomfort with lost autonomy. Qualitative work to explore ways to approach this, and develop platform research as part of ‘learning health systems’ would be valuable. Further, ensuring engagement with all stakeholders, as mentioned above, before starting a trial, will allow for effective completion.

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

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Background

Invasive Salmonella disease represents a major global health problem, estimated to affect over 27 million people annually and causing approximately 900,000 deaths.^{1,2} The major burden of disease occurs in South/South-East Asia and sub-Saharan Africa. The WHO has recently listed Salmonella as a “priority pathogen”, identified as one of 12 families of bacteria thought to pose the greatest risk to human health through rising antimicrobial resistance.³ Vaccination of populations at the highest risk of disease is likely to have the greatest impact on disease prevalence in the short-to-medium term.

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 has established a Salmonella controlled human infection model (CHIM) in UK healthy adult volunteers. This model has provided a unique opportunity to investigate mechanisms and determinants of immunity to Salmonella infection in a strictly monitored experimental setting.⁴ Importantly, the model has been used to accelerate the development of novel Vi-conjugate vaccines for typhoid fever, by testing their efficacy in healthy volunteer CHIM prior to on-going effectiveness studies in the field.⁴⁻⁶

Brief description of the research project

Whilst Salmonella CHIM have proven successful to date, it remains 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.

Volunteers in endemic countries are likely to differ from UK volunteers across a range of important variables such as previous Salmonella exposure, diet, intestinal microbiota, risk factors and genetic profile.⁷ These issues are particularly pertinent for invasive non-typhoidal Salmonella disease (iNTS), where chronic-malaria, sickle-cell disease, malnutrition and HIV infection represent major risk-factors.⁸ 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. Areas that could specifically benefit from conducting Salmonella CHIM in endemic settings include:

- Assessment of novel paratyphoid vaccines in South Asia.⁹
- Development of an iNTS challenge model in sub-Saharan Africa and subsequent vaccine assessment.¹⁰
- Assessment of novel diagnostics, particularly those based on measuring host-response to infection.¹¹

There is precedent for conducting challenge studies in low/middle income settings, including for enteric pathogens such as Shigella spp.^{12,13} The Salmonella model has an established safety profile in over 2000 volunteers and trial protocols could be readily transferred to new study sites.¹⁴

Ethical Issues

Participant safety and benefit: In the absence of adequate medical care, Salmonella infection poses a theoretical risk to study participants. The mortality of typhoid fever in the pre-antibiotic era was estimated to be ~30%, although this is reduced to <1% with prompt antibiotic therapy.¹⁵ The mortality rate of iNTS disease (for which no CHIM currently exists) is estimated at 20%.² With the exception of trials of testing candidate vaccines, early-stage CHIM models for Salmonella and other enteric pathogens may offer no direct benefit to participants to offset the predictable risks. The symptoms of typhoid (such as fever, headache and abdominal pain) will reliably occur in most participants and - whilst these symptoms are undoubtedly burdensome - their occurrence is expected and predictable. Volunteers can therefore be clearly informed about the risks they are likely to face prior to enrolment. Understanding of the risks could be improved by applying a multi-staged consent process that allows participants time to digest information and obtain answers to their questions. Additionally, tests of understanding could be administered, with feedback for incorrect responses.¹⁶

The risks to study participants could be increased in low income settings, owing to, for example, worse pre-morbid health status, increased risk from prior immune priming and increased risk of carriage. In the UK challenge model, several safeguards are implemented to ensure safety of participants, including detailed screening assessments, appropriate hospital facilities with capacity for inpatient admission and intensive care; dedicated staffing with 24/7 contact; prompt access to treatment, combined with adequate hygiene and sanitation precautions. Such safeguards would need to be at least as stringent should Salmonella CHIM be performed in low-income countries, which may limit the number of sites where such studies could be performed or require large infrastructure investments. Additionally, purchasing insurance for research-related harms that extend beyond the study period may be another important way to protect participants.¹⁷

Risk of transmission: In the absence of adequate personal hygiene, Salmonella and other enteric CHIM pose a theoretical risk of disease transmission to household contacts. The wider community may also be at risk in the absence of adequate sanitation infrastructure. These concerns are present in the UK, but are potentially amplified in low-income settings. Household contacts could be consented at face-to-face screening or by provision of written material, although consideration should be given as to how to proceed should a household member decline consent. In contrast, it is unfeasible to obtain consent from all individuals living in a community who may be at theoretical risk of acquiring infection. In the UK, consent to release potentially pathogenic bacteria into the environment is conducted under the observation of government bodies (e.g. Public Health England, DEFRA), and a similarly stringent level of environmental protection oversight might also be required in low-and-middle income countries. Community consultation to share information, learn the community's level of concern about these risks, and provide information about the way the study team will seek to minimize these risks may further be important for preserving public trust in CHIM studies and research more generally.

Transmission risks could be minimised by conducting these studies in an inpatient setting, where hand hygiene could be monitored and sanitation infrastructure guaranteed (e.g. flush toilets, waste treatment). In this scenario, participants would be confined to the inpatient facility until proven to be clear of infection. Whilst such an approach has been taken previously,^{12,13} several ethical uncertainties remain. For example, in UK trials, a period of approximately 6 weeks is required before an individual is considered clear of Salmonella infection after challenge. It may be impractical or unethical to confine an individual for this length of time and would be complicated if participants expressed a wish to withdraw from the study. Clear communication about such requirements in advance, along with fair compensation for such a long period of confinement are two ways to respect participants who are being asked to take on such a significant burden. But more analysis might be needed, including a clear justification for any limitations on volunteers' rights to withdraw from research, before proceeding.

Volunteer reimbursement: Safety monitoring in the Salmonella CHIM requires a large time commitment. Financial reimbursement in resource-rich countries is often set to a high level (e.g. \$3000-\$4000 for UK typhoid challenge studies), to account for potential loss of earnings. The time commitment required would increase even further if participants were to be confined as inpatients in low-income countries. The substantial reimbursement amounts inevitably raise concerns of undue inducement amongst financially vulnerable populations – a concern that is not confined to low-income countries. Some studies have suggested that volunteers who are financially motivated may pay particular attention to potential risks of participating in such studies.¹⁸ Nevertheless, reimbursement could be set at levels that achieve fair compensation for loss of earnings from time committed (e.g. equivalent to average local daily wage), but not necessarily proportional to perceived risks.

Engagement with local ethics committees: CHIM studies would likely attract intense scrutiny from research ethics committees in low-income countries, particularly in sites where such studies have never been previously undertaken. Such studies may be perceived as violating core ethical principles such as non-maleficence and may pose a reputational risk to the institution. Concerns may be allayed by open discussions between investigators involved with CHIM studies, independent study review by infectious disease clinicians along with training and support for ethics committees, provided by independent bodies.

Regulatory requirements and scrutiny of challenge agents: The choice of challenge strain and dose is a key variable in Salmonella CHIM studies. Stocks of Salmonella challenge strain are typically manufactured to a GMP-like standard to ensure safety and reproducibility, but are subject to different regulations between regions. For example, in the USA, microbial challenge agents are considered investigational medicinal products (IMPs) and, as such, are subject to scrutiny by the Food and Drug Administration. In contrast, EU legislation currently does not view challenge agents as IMPs. Drug review boards in many resource-limited settings may have to develop country-specific legislation to cover regulation of challenge strains. Early engagement with investigators and regulators in other countries will be necessary to ensure consistent regulatory guidelines that are country specific, ensure participant safety, whilst simultaneously avoiding hindering research programmes.

Conclusions

Salmonella challenge studies in low and middle-income countries are potentially both highly valuable and feasible, whilst also providing a platform to address an area of major global-health concern. In addition to addressing country-specific host and environmental factors relevant to vaccine testing, the establishment of Salmonella CHIM could increase research capacity, provide training of local staff in laboratory/research techniques and provide a platform to undertake novel CHIM studies for other enteric diseases. High levels of safety (coupled with careful consideration of country-specific ethical issues) must be maintained to ensure confidence in the model and to avoid reputational damage. Whilst Salmonella CHIM studies are well established in the UK setting, trial protocols and regulatory processes must be adapted to local circumstances and must take account of the different concerns that may arise in endemic settings. Only after a prolonged consultation period with local stakeholders to address any potential concerns and to ensure ownership of the model should such a challenge study move forward.

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

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Brief description of the research project

A Controlled Human Malaria Infection (CHMI) study in Kenya aims to assess human immunity to *Plasmodium falciparum* using sporozoites (PfSPZ Challenge) administered by direct venous inoculation. The entire study was expected to recruit 200 individuals across three challenge events. The 2nd challenge event in which the social science study was embedded screened 114 participants and enrolled 64 (49 male; 15 female).

A multi-stage information giving and consent process preceded the screening activity of the CHMI study; an eligible participant was only allowed to enroll into the study if they passed a test of understanding administered by a clinician. Once enrolled and inoculated with the malaria parasites, the participants were in-residence at a guesthouse within a local university for an average of 18 days (range 15-24 days). A total of 320 mls of blood were drawn from each participant after screening up to end of in-patient stay. The length of participant in-patient stay was dependent on whether they had achieved a threshold of parasites before 21 days (at which point they were treated and discharged); if not, they would remain at the residence until day 21 and then be treated and discharged. All treatments were directly observed by the clinical team.

The social science sub-study aimed to explore participant' experiences, their understanding of the malaria challenge study, and motivations for participation. Data collection included participant observation of research activities, 5 Focus Group Discussions (FGDs) with 36 participants segregated by gender (2 FGDs with 14 females and 3 FGDs with 22 males); and 2 in-depth interviews with study team members. A thematic content approach was used to analyze the data, with an iterative process of coding building into categories and themes that were then applied to the entire dataset.

Background

CHMI studies have repeatedly and successfully been conducted for many years in developed countries (Europe, United States, Australia, Colombia¹), but only a handful have been recently conducted in Africa, including Kenya.²⁻⁴ Reasons for this imbalance include a lack of proper infrastructure to produce parasite cultures in many parts of Africa, and inadequate facilities and expertise to conduct such studies safely.^{3,5} Challenge studies raise numerous ethical concerns, including whether it is ethically acceptable to deliberately inject people with disease-causing pathogens⁶, concerns about lengthy confinement of participants for safety monitoring, and that the high levels of compensation might blind people to the significant risks and burdens involved.^{5,7,8} Despite these issues, challenge studies have not received much explicit attention in existing international and national guidelines for clinical research^{7,8}; and there has been limited, if any, associated empirical ethics work in LMIC. We conducted a social science study to explore the experiences and perceptions of participants regarding their participation in a malaria challenge study on the Kenyan Coast. In our study, some ethical concerns were not borne out, but others raised important challenges for future research.

Ethical issues

Risks associated with challenge studies: The risks associated with the challenge study were described in detail in consent forms and information giving sessions. They included the potential to become sick from malaria parasites injected into the body, a low risk of infection at the site of blood draws, inconveniences associated with extended stays in the hostel facility, and related travel costs. Participants seemed to appreciate the risks associated with pathogen and were aware that they will be treated if they did get ill. They also categorically stated that they would not have participated in a challenge study whose pathogen had no cure.

Compensation for study participation: For the CHMI study, there was careful consideration of appropriate levels of compensation for time and inconvenience to participants, guided by institutional guidelines and discussions with researchers and ethicists at the Institute. A challenge voiced in all discussions during protocol review was determining appropriate levels of compensation for inconveniences experienced by healthy participants not receiving direct benefit who would be in-patient for almost a month. Eventually a compensation of approximately 20 USD per in-patient stay was seen as fair, in addition to full-board stay in the hostels in one of the local Universities. This amount was higher than standard compensation for daily involvement in research activities not requiring in-patient stays. Participants spoke very positively about the level of compensation, although many indicated the amount was equivalent to what they usually earn in their casual employment; the difference was that they would receive the amount as a lump sum at the end of the in-patient stay, while income from casual work is unpredictable. Receiving the amount as lump sum was viewed very positively as participants planned several projects (e.g. paying school fees, starting business, paying off loans etc.). Despite the rate appearing attractive to participants, they did not appear to ignore the risks and described the key elements of the study in ways that showed they understood what the study was about with only one exception that will be discussed below. Another factor that participants appreciated about the study was knowing one's health status following screening as some of the tests done would have been too expensive for them to undertake on their own. A few participants also mentioned altruistic reasons for participation, i.e. being able to contribute to finding a vaccine for future generations for a disease that is a huge problem in the area.

Informed consent: Although participants in the CHMI study were not highly educated, they generally said that they understood the information provided in the informed consent and spoke positively of the processes followed. A challenge they voiced was conceptualizing the volume and frequency of blood sample draws – while they had been informed of these, most felt that the blood volumes seemed much larger in reality than the explanations that had been given; they suggested having visual representations of the amount of blood volumes for future studies. Given sensitivities about blood samples in this community, we were surprised that participants had not keenly listened/understood about the blood samples at information giving sessions, and suspect that there might have been a level of crowding out some of the other study information, especially if participants were more interested in other aspects of information, such as levels of compensation. Clearly visualizing some of the consent information, as was suggested, may strengthen understanding of study information.

Community engagement: A vibrant community engagement programme is implemented at the Research Centre⁹, a platform used by the challenge study to engage key stakeholders including community leaders. CHMI studies seem remarkably different from other types of research in the sense that they involve infecting healthy people with disease; there is therefore need to constantly be aware of any emerging concerns or confusions and to address these promptly. Some of the issues that were raised and addressed immediately were clarifying that the challenge study was about malaria and not HIV. On-going rumours about the work of the Programme were raised on a few occasions and addressed by the participants and study teams. Given the low number of participants needed for challenge studies and the relatively high compensation, some participants were aware that their participation may have aroused jealousies among those who were screened out or were never invited. This is an area that we aim to explore during the next challenge event. We will also track the implications of the relatively high compensation levels on community responses to other studies being conducted in the area.

Commentary

From this relatively small social science study embedded in an ongoing CHMI study, some areas for ethical consideration emerge: 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. If challenge studies are to be conducted in resource limited settings with poorly performing health infrastructure and care systems, these issues should be taken into account and may require re-visiting existing ethical guidance and frameworks. Further empirical research ethics work is also needed to clarify what ethical concerns arise over time, and when challenge studies are conducted in resource-limited settings across different challenge models.

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

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Brief description of the research project

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 enroll healthy volunteers who would not otherwise be exposed to Zika virus. Previous exposure to other flaviviruses (such as dengue, yellow fever, West Nile) and would have been an exclusion criterion for the study. 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. The panel included ethicists with expertise in several subfields of research ethics (i.e., the ethics of human challenge trials, study design, translational and early phase research, and research with pregnant women), a neurologist, two obstetrician/gynecologists, and an infectious disease physician. Conflicts of interest included being an employee of federal agencies who might sponsor or review a Zika virus human challenge trial or a researcher who might conduct a Zika virus human challenge trial. The panel held several teleconferences, an in-person meeting in Rockville, Maryland on December 12, 2016, and deliberations in person and over teleconferences, and ultimately drafted a report that was published in February 2017.

Background

In 2015, Zika virus emerged as a major public health crisis in Brazil and other South American and Caribbean countries. Although the World Health Organization declared the state of emergency surrounding Zika virus over in November 2016, it indicated that Zika is likely to be a persistent and unpredictable public health threat for years to come.¹ Zika is an infectious disease with potentially devastating consequences, including congenital Zika syndrome in infants, and Guillain-Barré syndrome and cardiac issues in adults.²⁻⁶ Zika virus can be transmitted through mosquito vectors, sexual transmission, and mother-to-child transmission.⁷ Despite the best efforts of researchers around the world to understand this disease, first described in 1940s, a great deal of uncertainty remains about the transmission of Zika virus and the range and severity of complications that can result. For instance, some cases of Zika virus appear to have involved transmission several months after infection.⁷ One case of transmission from a very ill father to his son who was caring for him has raised unanswered questions about the route of transmission.⁸

Ethical issues

The Zika HCT ethics expert panel produced a report in early 2017 that offers a preliminary ethical framework for a Zika HCT. This report concluded that a Zika virus HCT could be ethically justified in principle, but would be premature at the time.⁹ Although the panel raised several ethical issues that should be addressed, we will focus on three of the most pressing ethical issues here. First, should there be an upper limit on risk even if participants give their consent? Second, a Zika HCT poses risks to both research participants and bystanders. How can risks to people who may not know or give consent to being exposed to risk of infection with Zika virus be justified? Third, the trial was proposed in a non-endemic setting, but there may have been some ethical advantages to conducting it in an endemic setting. All things considered, what setting would be best for a Zika HCT?

Upper limit on risk in research: Most research ethics guidelines and regulations do not set an explicit upper limit of risk in research with consenting adults, as long as they understand the risks and the research has sufficient scientific and social value to justify the risks.¹⁰ One notable exception is the Nuremberg Code, which stipulates that “no experiment should be conducted, where there is an a priori reason to believe that death or disabling injury will occur.”¹¹ Many ethicists would agree with this position and argue that there should be some upper limit of risk in research; however, there is no clear consensus as to what that limit should be.¹⁰ Perhaps the most promising approach to defining this limit is by analogy to the risks of other voluntary and socially valuable activities that competent adults can give their consent to, such as volunteer emergency medical assistance, living kidney

donation, or blood donation. Yet more work needs to be done to choose comparators that are ethically appropriate and define an upper limit of research risk.¹² Assessing the risks of a Zika HCT is further complicated by the fact that there are many unknowns about Zika virus and its complications, making the potential harms of being infected with Zika virus highly uncertain. The Zika HCT ethics panel compared the risks of a proposed Zika HCT to other types of research with healthy volunteers, such as phase I drug/vaccine trials and malaria infection challenge studies, and concluded that a Zika HCT does not pose much higher risk to participants than research that is already being conducted and has gone through channels of ethics and regulatory approvals.⁹ Ultimately, the panel did not think that the level of risk to participants should necessarily prevent a Zika HCT from going forward, but remained concerned about the level of risk to bystanders outside of the research study.

Bystander risk: A Zika HCT could expose individuals outside of the research to Zika virus, such as household contacts or sexual partners of participants, or their offspring. Since people may choose their sexual partners spontaneously or anonymously, it would be difficult to identify every sexual contact of a research participant in advance and obtain their informed and voluntary consent. Even if sexual partners could be identified, informing them about their partner's participation in research and giving them veto power raises additional ethical questions. Moreover, potentially affected offspring and other bystanders lacking decisional capacity could not give their consent. The panel highlighted the importance of minimizing the risk of transmission of Zika virus to others outside of the research setting, and suggested several ways to minimize risk of transmission.⁹ Assuming that there is still some level of risk that cannot be eliminated, how can risks to bystanders be justified? Ethicists have argued that although bystander risk is not addressed by research ethics guidelines or regulations, consent from identifiable bystanders would be ideal, while both identifiable and non-identifiable bystanders who cannot be asked for their consent should be protected from research risk.^{13,14} The panel ultimately concluded that only near-zero risk to bystanders should be tolerated in a Zika HCT since obtaining their consent was prohibitively difficult, and if bystanders were harmed in the course of a Zika HCT, this could threaten public trust in research more generally.

Endemic settings vs. non-endemic settings: The proposed Zika HCT was to be conducted in non-endemic settings. The researchers who proposed the trial were accustomed to conducting challenge trials at their institutions and had the resources and facilities to conduct the trials there. Conducting the trial in an endemic setting could have some advantages, however. Individuals in an endemic setting might have more awareness of the effects of the disease and more likely to want to participate for altruistic reasons or out of a sense of solidarity. Conducting research in a way that is responsive to a host community's priorities is one possible way to justify higher risk research and can be useful for building capacity in resource-limited settings to conduct research in the future.¹⁵ Finally, if people are already at risk of being infected with Zika virus, the risks of being infected with Zika virus in a human challenge trial could, in theory, be discounted given that they have some baseline risk. This "relative" approach to assessing risk in research is controversial, however, because it could take existing unfairness as a justification for conducting risky research in a way that exacerbates injustice.¹⁶ On the other hand, one concern about conducting Zika virus research in an endemic setting is that if the virus spreads outside of the study, it could start a new outbreak. In addition, the potential exposure of participants to natural infection with Zika virus could threaten the scientific integrity of the study. In the end, the panel suggested that conducting a Zika HCT in an endemic setting might be preferable if the risks of spreading Zika virus beyond the study could be minimized to near-zero, but noted that the feasibility of this was unclear.

Commentary and conclusions

This case of a Zika virus HCT raises important questions for future HCTs and suggests that a revised ethical framework is needed to address unresolved issues. In particular, questions about 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 are unanswered questions for future research.

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Guidance and regulation sessions

Theme 5

Presentation: **Current international ethical guidance on alternative research designs**

Rieke van der Graaf, PhD, UMC Utrecht, Julius Center, Netherlands

Although the randomized controlled trial remains the gold standard in clinical research, the interest in alternative research designs is growing, also in low-resource settings. At the same time, international guidance documents on these alternative research designs are limited. In this session, I will identify the ethical guidance mentioned in the current international ethical guidance documents. I will focus on the ethics related to the use of cluster randomized trials, stepped wedge cluster randomized trials, adaptive platform trials and controlled human infection models (CHIMs), in particular related to the use of these designs in low resource settings.

The Ottawa Statement and the CIOMS International ethical guidelines for health-related research have guidelines for cluster randomized trials (including stepped wedge designs), but limited specific guidance for the use of these designs in low resource settings. There is no international guidance for the use of platform trials. Finally, WHO has a document on the use of CHIMs. In addition to these formal documents, there are a few papers in the form of reviews and reports which mention ethical issues to be considered when using alternative trial designs.

The literature reveals several open ethical issues in the use of alternative trial designs, in particular related to informed consent, social value and risk-benefit assessments.

The combination of growing international interest in alternative designs, scarce international ethical guidance, and open ethical issues implies a need for more ethical guidance. Uptake of ethical guidance documents is crucially dependent on the willingness of international organizations to assist in developing and issuing these documents.

Presentation: **CHIMS: What does it mean to be a responsible research funder?**

Katherine Littler, Wellcome, UK

The use of controlled human infection models (CHIM) has the potential to accelerate the development of vaccines with significant public health relevance, and is particularly useful for identifying promising vaccine candidates suitable for evaluation in large-scale field trials. As part of Wellcome's Vaccines Programme strategy, we are looking to support the expansion of CHIM to accelerate vaccine design and development for target populations, including capacity building for CHIM in disease endemic regions. Despite the scientific importance of these studies, there is limited bioethical discussion and guidance to assist stakeholders, including funders, institutional review boards, ethics review committees and researchers, in considering different issues raised by research that involves purposefully infecting healthy volunteers. One way Wellcome is working to understand the issues that CHIMs raise is through the support of a comparative review of previous CHIM studies taking place in a variety of contexts, to identify different ethical, governance and regulatory challenges that may have arisen. This will provide evidence to support the development and implementation of an ethical framework for considering CHIM.

In addition, in line with funders and sponsors' responsibility to support innovation that promotes and sustains the public good, we are looking to develop a set of standards and guiding principles for CHIM. We believe that these types of principles will establish high standards in research practice, aimed at safeguarding volunteers, promoting suitable engagement practices and governance mechanisms that will build confidence in the appropriate use of CHIMS. What else needs to be done to actualise and underpin these principles needs further exploration, as does the broader question of what types of research, trials and innovations should merit funder principles and specific ethical frameworks?

Respondent: **Ethical challenges in the review of clinical trials using alternative trial designs in the low and middle income countries: A case of ethical guidelines used in the East African region.**

Claude Kirimuhuzya, Kampala International University, Uganda

Robust evaluation of new therapies in humans has traditionally been based on individually Randomised Clinical Trials (RCTs) as the "gold standard" and ethical review guidelines used by the regulatory bodies have been based on this standard. However, adaptive trial designs in which randomisation is group- based rather than being at individual level, have recently become increasingly popular, and this presented ethical challenges. The objective of the case study was, therefore, to determine the extent to which the ethics guidelines in the East African Region address the ethical issues related to alternative trial designs.

The case was a review of the ethical guidelines from Kenya, Rwanda, Uganda, Sudan and Tanzania. The review concentrated on issues regarding Clinical equipoise, the informed consent process, and compensation of the research participants.

The results revealed that all the guidelines in the region are based on RCTs as the "gold standard" with no reference to the alternative trial designs and that they also serve as the basis for the training and operations of members of ethics bodies. The guidelines emphasise that there must be clinical equipoise, informed and voluntary consent, and compensation for research participants. The use of alternative trial designs presents ethical challenges to both the regulators and the researchers since it can lead to rejection of important trials or approval of inappropriate trial designs, due to lack of relevant expertise, if the status quo is not changed.

As a way forward, there should be: 1) Review of the current guidelines to identify the gaps that need be filled; 2) Conduction of research among the members of the regulatory bodies and researchers in the region to ascertain the actual skills and expertise in relation to adaptive clinical trial designs; and 3) Revision of the current ethical guidelines to accommodate the new trial designs.

Respondent: **Current guidance on alternative trial designs: A critique from the Caribbean**

Derrick Aarons, The Caribbean Public Health Agency

Very scant guidance currently exists on alternative clinical trials methods and designs. CIOMS Guideline 20 on Research in Disasters and Disease Outbreaks has only one paragraph devoted to the subject. Guideline 21 on Cluster Randomized Trials provides more guidance, but only on this particular form of alternative research design. The Ottawa Statement on the Ethical Design and Conduct of Cluster Randomized Trials (CRTs) provides significant detail, but only in regard to CRTs and not on other designs such as stepped wedge trials, adaptive trials, and controlled human infection models.

The broad concepts and special considerations associated with alternative trial designs have not been introduced to most of the research stakeholders within the 24-member states of the Caribbean. Currently, the only guidance on human subjects research with which most researchers, research ethics committees (RECs), and other research stakeholders in the Caribbean are familiar are the Declarations of Helsinki, the Belmont Report (and the ‘common rule’ in the USA), and to a lesser extent, the CIOMS Guidelines. Consequently, without a clear understanding of the concepts involved, members of research ethics committees in the Caribbean will find it difficult to properly assess any proposed research that use an alternative trial design.

Further, only two (2) of our 24-member states in the Caribbean currently have any regulation to protect the participants of research and provide compensation if harm from research occurs. Accordingly, great challenges would exist for us in the ethics review and conducting of alternative clinical trials, and so much more exposure and enlightenment will be needed before this form of research is accepted as being scientifically valid by the various research stakeholders in the Caribbean.

Respondent: **Guidance and justification for novel trial designs: A reflection from Latin America**

Carla Saenz, Pan American Health Organisation

Discussions with Latin American scientists, ethicists, members of ethics review committees, regulators, and health authorities reveal that dealing with increasingly popular novel study designs is being perceived as challenging primarily due to the lack of relevant local expertise. No specific regulations addressing these designs exist, which is arguably not a weakness: the analysis of this level of granularity is better conducted at the level of ethics review committees, on the basis of specific protocols and up-to-date international ethical guidelines. Yet relevant ethics guidance is not always available or known. Furthermore, there is a tendency to think that an entirely new ethics guidance is needed to conduct an ethics analysis of these novel study designs, as opposed to one that focuses on their morally relevant features.

From a regional perspective I want to highlight that a discussion about the specific ethics guidance for these designs should be preceded by discussion of why some of these designs are needed or preferable to their standard alternatives. This is a reflection that was initiated with some Latin American participants towards the end of the 2015 GFBR meeting. Many of us worry that some assumptions have been made too quickly in response to the Ebola outbreak. It is however imperative that we pause to analyze the justifications for using some of these designs, taking into account that “X is ethical,” “X is feasible,” and “X is what people support” are different claims, and then determine the best way to respond to the problem at stake. We as experts have the moral duty to clarify these differences, and to ensure that communities, research participants, scientists, and health authorities are not making decisions based on wrong claims, incomplete information or therapeutic misconception, but on evidence and a rigorous ethics analysis that we must provide.

Respondent: **Current ethical guidance and regulations in Southeast Asia**

Cristina E. Torres, FERCAP Coordinator

Current ethical guidelines and regulations in Southeast Asia focus on the ethical review infrastructure (e.g. IRB/ REC membership, roles and functions, training, etc.) and standard generic issues (e.g. risks, benefits, informed consent, etc.) to be reviewed by the research ethics committees. The national accreditation of RECs had been initiated in Taiwan, the Philippines and Thailand, at the same time that the Forum for Ethical Review Committees in Asia and the Pacific (FERCAP) had expanded its certification/ recognition of qualified IRBs to include approximately 220 RECs in 12 countries as of 2017. Because Good Clinical Practice (GCP) inspections are being done by the regulators (US FDA, European Medicines Agency, etc.) of pharmaceutical sponsored research for investigational medicinal products (IMP), the IRBs are compelled to improve GCP compliance of their sites to avoid deviations/ violations. The review of randomized clinical trials in drug development has become standard fare among hospital IRBs chosen as sites for multicenter trials for new drugs or interventions.

Most IRBs in Southeast Asia have little experience reviewing community based research, cluster randomized trials, public health and health systems research as well as socio-behavioral research. It may probably be attributed to public health, social science researchers not feeling compelled to submit their protocols for ethics review.

Current ethical national guidelines and regulations that have been formulated with the help of IRB members do not clearly differentiate between clinical research vs. public health or behavioral research. While vulnerabilities may be assumed or identified, there is no in-depth guidance for the analysis of risks and benefits nor are the informed consent issues properly differentiated and analyzed. Despite CIOMS, the Ottawa Statement and other similar guidance, ethics review and national guidelines and regulations are basically straight forward that miss the refinements necessary in the review of innovative design and community based interventions.

However, due to the increasing popularity of public health and community based researches, there is need to address the knowledge gap to improve the ethics infrastructure in Southeast Asia. There is need to conduct continuing ethics education of research stakeholders that includes sponsors, investigators, REC members, regulators and the general public.

Theme 6

Presentation: **Informing ethical evaluations of adaptive clinical trials through simulation**

Roger Lewis, University of California

Description of the Project

One adaptive clinical trial innovation that can be used in low and middle income countries (LMICs) is response-adaptive randomization (RAR), a technique by which information that accrues early in the trial is used to modify the randomization proportions used to assign treatments to later patients, in a way that improves the expected outcomes of patients treated later in the trial. In order to enable a more informative discussion of the ethical advantages and potential disadvantages of RAR, simulations of alternative clinical trial designs--some including RAR and some not--under a variety of assumptions regarding potential epidemic scenarios can be highly informative. In this project, we have conducted extensive simulations of traditional and innovative trial designs that allows us to illustrate the impact of trial design decisions on the ethical and risk-balance profile from the perspectives of participants and society. These can be used to inform those designing clinical trial for LMICs and those considering whether they, or their communities, should participate.

Background

An adaptive clinical trial innovation that can be used in low and middle income countries (LMICs) is response-adaptive randomization (RAR), a technique by which information that accrues early in the trial is used to modify the randomization proportions used to assign treatments to later patients, in a way that improves the expected outcomes of patients treated later in the trial. In essence, this approach implements a continual learning environment, through which information gained early in the trial is used to improve the outcomes of patients treated later in the trial, in a way that preserves the statistical and scientific integrity of the clinical trial. This approach can be used to improve the risk-benefit balance for participants in the trial, an issue that may be of particular concern in the setting life-threatening pandemics, and when the affected population has little experience with clinical research and randomization.

A number of concerns have been raised recently regarding the ethics of RAR, despite the fact that this technique is often used with the specific intent to improve the risk-benefit profile for patients participating in the trial. These debates have largely been hypothetical in nature or have been based on highly selected examples that are not generally informative.

To enable a more informed and productive discussion of the ethical advantages and potential disadvantages of RAR, we have conducted detailed simulations of a variety of clinical trial designs--some including RAR and some not--under a variety of assumptions regarding potential epidemic scenarios. These scenarios can include situations in which the epidemic comes and goes very quickly or it persists over a long period of time, and situations in which there are single or multiple treatments being investigated. The results of computer simulations demonstrate that the ethical advantages and potential disadvantages of RAR depend on the specifics of the clinical trial setting and that broad generalizations are not possible.

Frequently, investigators have considered specific, prior clinical trial experiences to gain insights into what trial design strategies should be used for future trials. While there is value in the investigation of specific case studies, perhaps based on single examples or even specific data streams that were accrued during completed clinical trials, the ethical characteristics of clinical trial designs can only be thoroughly investigated through the investigation of their performance over a wide variety of potential scenarios. The art and science of clinical trial design involves creating a trial that performs well, from both scientific and ethical perspectives, over a wide range of potential future events, rather than just a single future event that is envisioned or may have been observed. Thus, realistic and detailed computer simulations greatly extend the information that can be used to select an appropriate clinical trial design for a LMIC setting.

Ethical Issues

Simulations of alternative clinical trials designs can be used to address numerous ethical questions, including:

- Under what circumstances is response-adaptive randomization (RAR) advantageous from either an individual or a societal perspective? When is it disadvantageous?
- Given that a thorough understanding of the advantages and disadvantages of alternative clinical trial designs must be well understood by all stakeholders, including those implementing the trials and those participating as research subjects, how can we best illustrate and communicate properties of alternative, innovative designs to all stakeholders?
- How do we create and tailor innovative trial designs to be ethically and scientifically appropriate, given the tremendous uncertainty about future characteristics of diseases, populations, and available therapies?
- How do we supplement the lessons learned from prior research experience in LMICs to address what may or may not happen in the future?
- How do the ethical characteristics of innovative trial designs vary from individual and societal perspectives?

Commentary: Conclusions and Recommendations for Future Work

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.

Future work should address:

- How can we best use clinical trial simulation to communicate with and inform all clinical research stakeholders in LMICs?
- Should simulation be considered a necessary part of evaluating an innovative trial design for use in LMICs?
- How can current trial simulation approaches be improved to make them more available and useful to those working in LMIC

Poster Summaries

- 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)

1. Implementation of the Clinical Practice Guidelines (CPG) for the Elimination of Maternal Child Transmission (ETMI) of Syphilis / HIV, Colombia

Jackeline Bravo, International Center for Medical Research and Training, Colombia

Brief description of the research project

The elimination of the mother-to-child transmission of syphilis / HIV is the cornerstone of screening and timely treatment. However, the lack of understanding of the regulatory component, the administrative barriers faced by pregnant women to initiate prenatal care, the lack of standardization of new processes in the care pathway, the lack of access to treatment at the primary level, the clinical concepts outdated and new methods of diagnosis, poor adaptation of quality assurance processes in the clinical laboratory, impose greater challenges to the goal of elimination.

The overall goal of this project seeks to promote the effective implementation of CPGs in the Plan of Elimination of Maternal Childhood Transmission of Syphilis / HIV in two Health facility level in Colombia. The project is based on the co-design of the organizational and clinical processes for the implementation of the recommendations of the CPGs with the actors involved, and the evaluation of the adaptation and acceptance of this design by the executors and beneficiaries of the services. This study will be developed with an interdisciplinary team of national and international researchers and new researchers in the areas of epidemiology, public health, pediatric nurses, gynecology, administrators, industrial engineers, in conjunction with prenatal care team, clinical laboratory, service delivery and administrative of two Health facility level.

Background – relevant facts about the host country/community and disease studied

The elimination of maternal and child transmission of syphilis / HIV in Colombia is a goal proposed in the ten-year public health plan 2012-2021, which proposes by 2022, to reach and maintain the percentage of mother-to-child transmission of HIV at 2% or less and to have reached and maintained the incidence of congenital syphilis in 0.5 cases or less, including stillbirths, per 1,000 live births.

In 2014, 17,400 cases of congenital syphilis were reported in the Americas (data from 32 countries), and a rate of 1.3 cases per 1000 live births. Colombia has shown progress, but the goal of eliminating IMT from syphilis / HIV has not been met.¹

The number of new HIV infections in children aged 0-14 fell between 2000 and 2014 by 78%, which means that by 2014 there were 2,500 new HIV infections in children in Latin America and the Caribbean. In Valle del Cauca perinatal transmission for 2015 was 1.9%. For the city of Cali this perinatal HIV transmission is 0.5%.²

Ethical issue related with Implementation Research Design

1) Stepped Wedge Designs:

One specific aim in this project is to arrange a design of the processes necessary to optimize the implementation of the recommendations of the CPGs. Principal investigator proposes an iterative process of learning and continuous adjustment during the different stages of implementation. The effects of the implementation with interrupted time series will be evaluated; the results will be controlled over time and may have interruptions after an intervention, performing a regression and analyzing the results in a staggered form, as more IPS (health facility level) is integrated with the new proposed intervention. The evaluation of the indicators is made before the start of the intervention in all the IPS (health facility level), to evaluate the changes as the IPS is incorporated to the new intervention and until all the proposed IPS (health facility level), have been included.

Commentary on the issues

Three arguments are usually invoked in favour of stepped wedge cluster randomized controlled trials: the logistic convenience of implementing an intervention in phases, the ethical benefit of providing the intervention to all clusters, and the potential to enhance the social acceptability of cluster randomised controlled trials. Are these alleged benefits real?³ I invite reflection about only two points: the study should allow that intervention activities are organized according to a randomized sequence, estimating time lags in implementation and effects, and accommodating policy changes during the trial period. This design requires equipoise: without it, randomizing participants to a control condition, even for a short time, remains problematic. In stepped wedge trials, equipoise is likely to lie in the degree of effect, effectiveness in a specific operational milieu, and the balance of benefit and harm, including the social value of better evaluation.⁴

2) Quasi-experimental study:

The second specific aim in this project is to compare the effectiveness of the interventions proposed by the CPGs for the elimination of syphilis / HIV, with the current practices in two health facilities level in Colombia. Principal investigator proposes to compare two arms: one of them will receive training, the new diagnostic method (rapid test) and all the recommendations of the CPGs; the control arm will be the current intervention ie. the set of prenatal control procedures for syphilis / HIV; in the early stages these groups do not receive the intervention and therefore are analogous to controls, which may pose an ethical challenge even if short-term because some participants are deprived of the proven intervention. It is called into question the autonomy and informed consent.

Commentary on the issues

A key principle driving the ethics of clinical research in humans is individual autonomy. In public health research autonomy has two dimensions, one concerns individual autonomy and the other concerns relational autonomy in the context of the community to which the individual and the health system belong. Informed consent is the process through which a research participant can exercise their autonomy.⁵ In this study it would seem that an individual may not have the chance to decide and give consent to randomization as randomization happens at the cluster level.

Principal investigator says that "... it will apply consent before and after randomization to patients and health-care workers..." but who are the research subjects? Who should be consented? It could be necessary to adapt the informed consent differently from traditional individual consent in clinical trial. Should some groups of participants be exempted from informed consent? Why? Which groups?

On the other hand, have the participants the option to refuse participation and visit other IPS (health facility level), to receive the conventional process? Challenges in operationalizing informed consent in the context of Implementation Research also include whether the beneficiaries are individual or population, and appropriate identification of who the actual research participants are.⁶

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2. (In)adequacy of the guidelines and policies in addressing alternative clinical trials in Kenya

Nderitu Wanjeri, Egerton University, Kenya

Kenya is one of the low-and middle-income countries (LMICs) in the world. Studies have shown that a number of health researches take place in LMICs and as such there should be proper guidance on how such researches should be regulated. In Kenya, there are specific ethical guidelines and policies that are meant to offer oversight on how research should be conducted. This proposal critically analyses three main national guidelines which address aspects of guidance from different perspectives. These are: i) Guidelines for Ethical Conduct of Biomedical Research Involving Human Subjects in Kenya (2004) ii) Kenya National Guidelines for Research and Development of HIV/AIDS Vaccines (2005) iii) Guidelines for Applications to Conduct Clinical Trials in Kenya (2011). Specifically, the criticisms are based on the ability of these guidelines to give direction on the conduct of alternative clinical trials in Kenya.

i) Guidelines for Ethical Conduct of Biomedical Research Involving Human Subjects in Kenya (2004)

This is a document of the National Council for Science, Technology and Innovation (NACOSTI). NACOSTI is a statutory body in Kenya established under the Science and Technology Act of 1979. Any research planned to be undertaken in the country requires clearance and authorization through NACOSTI. The document gives general research and ethical guidelines for conducting biomedical research involving human beings in Kenya using internationally recognized reference materials. It also gives direction as to how to constitute an ethical committee in terms of membership requirement, appointments, offices, quorum requirements and education for Ethical Committee members.

On the issue of clinical trial designs and methods, the guideline document points out general direction on what constitutes an ethically sound research in terms of scientific validity (pg. 3), how research must conform to generally accepted scientific principles and must be based on laboratory and animal experimentation and a thorough knowledge of the scientific literature in the area of the research (pg. 10) and that the design and performance of each experimental procedure involving human subjects must be clearly formulated in an experimental protocol (pg. 10).

But it offers some direction about randomized controlled clinical trial under the explanation on the phases of clinical drug and vaccines trials (pg. 15). As such the document enumerates that Phase II of drug investigation consists of controlled clinical trials designed to demonstrate effectiveness and relative safety. Normally, these are performed on a limited number of closely monitored patients.

ii) Kenya National Guidelines for Research and Development of HIV/AIDS Vaccines (2005)

These are guidelines given by the Ministry of Health of the Republic of Kenya as part of the role of the government to create an enabling environment for the successful conduct of HIV/AIDS vaccine trials in Kenya though providing a framework for developing and evaluating HIV/AIDS vaccines. The guidelines direct that Phase III trials are usually double-blind placebo-controlled trials, involving thousands of volunteers at higher risk of HIV infection. They present a number of scientific, logistic and ethical problems (pg. 8).

iii) Guidelines for Applications to Conduct Clinical Trials in Kenya (2011)

These guidelines are given by the Expert Committee on Clinical Trials (ECCT) of the Pharmacy and Poisons Board established under the Ministry of Health in Kenya. A major function of the ECCT is to review all clinical trial protocols on investigational products (pharmaceuticals) and medical devices to be conducted in Kenya and to provide recommendations to the Board. The ECCT has developed checklists and guidelines for submission of protocols. Under the Clinical Trial Protocol the guideline enumerates about the Trial Design (pg. 20) whereby it requires the principal investigators to give a description of the type/design of trial to be conducted and the examples given there include double-blind, placebo-controlled and parallel design. These

are the conventional randomized controlled clinical designs which are common in many clinical and drug trial studies in Kenya.

Commentary, Conclusion and Recommendation

The above guidelines and policy documents give a clear direction that clinical and drug trials in Kenya adapts the conventional randomized controlled designs and methods. They do not seem to be giving much attention to the alternative clinical trial designs which are on the increase as methods of conducting trials and their resultant ethical issues. The NACOSTI guidelines only point out that any alternative procedures or courses of treatment that might be as advantageous to the subject as the procedure or treatment being tested must be clearly explained to the potential participant in a study (pg. 11). The *Kenya National Guidelines for Research and Development of HIV/AIDS Vaccines (2005)* in its section on the informed consent checklist at the appendices (pg. 52) include two items that may point to a similar directive as the NACOSTI guidelines. This includes a) A disclosure of appropriate alternative procedures or courses of treatments, if any, that may be advantageous to the subject, b) The alternative procedure(s) or course(s) of treatment that may be available to the subject, and their important potential benefits and risks. *The Guidelines for Applications to Conduct Clinical Trials in Kenya (2011)* have not as such given any direction as to how alternative procedures may be handled or presented during the conduct of clinical trials in Kenya.

It can therefore be concluded that most of the clinical and drug trials being conducted in Kenya take the model of randomized controlled designs which are well directed within the available Kenyan research and ethical guidelines. However, the situation of Kenya, with its unique context due to the some socio-cultural realities, low economy and high disease burden which therefore attracts a lot of clinical researches, does not have comprehensive research and ethical guidelines which includes guidelines on alternative clinical trials which such a unique context would require most.

As matter of recommendation therefore, this proposal suggests that alternative clinical trial designs and methods be emphasized and guidelines to that effect, both research and ethical, be developed in Kenyan as a complement to the regular randomized controlled clinical trial designs so that in the specific and unique contexts that characterize the Kenyan reality may be addressed comprehensively. More research on this need would bring this aspect into perspective.

3. Developing participant safety plans for research involving network randomization and stigma

Jeremy Sugarman (Berman Institute of Bioethics, US), Mark Barnes, Scott Rose, Konstantin Dumchev, Tran Viet Ha, Riza Sarasvita, Irving Hoffman, William C. Miller

Context: HPTN (HIV Prevention Trials Network) 074, “Integrated Treatment and Prevention for People Who Inject Drugs: A Vanguard Study for a Network-based Randomized HIV Prevention Trial Comparing an Integrated Intervention Including Supported Antiretroviral Therapy to the Standard of Care” [NCT02935296] involves random assignment of injection networks in Indonesia, Ukraine, and Vietnam. In these sites, injection drug use contributes to high rates of HIV-infection, warranting the development of evidence-based approaches to prevention and treatment. However, drug use and HIV are highly stigmatized in these same settings, raising questions about whether it is safe and appropriate to conduct this research. Randomizing networks rather than individual participants adds additional complexity. Therefore, a formalized, multistage process was taken to help assess the feasibility of participant safety in the research and to develop procedures to minimize risk and to respond to social harms that might occur during it. Of note, these activities supplemented standard approaches to community engagement and consultation as well as local Institutional Review Board oversight at each site.

Commentary: Following initial site selection, the legal and social risks of the research were identified in two phases. First, a local legal/policy assessment was conducted by local experts at each site, roughly following the American Bar Association’s Rule of Law Initiative. Second, site teams conducted a series of semi-structured qualitative interviews with key stakeholders (such as people who inject drugs, clinicians involved with treating drug use or HIV-infection, law enforcement officials, and those with expertise on national drug policies) at each site to help place this formal policy review into context and to identify potential risks that might be related to participation in the research. Interview topics included: 1) social attitudes and access to care; 2) law enforcement actions; and 3) research participation. The findings from all sites were reviewed by study leadership, the Ethics Working Group Representative to the protocol and an Ethics Working Group member with international legal expertise. Where needed, additional information was requested from the local experts and study teams. Based on the aggregate information obtained, Participant Safety Plans were then developed at each site reviewed by study leadership and the Ethics Working Group representatives, refined and then implemented. Finally, in order to help identify any problems associated with research participation, social harms were assessed at each study visit. Enrollment in the trial is now complete. Although the trial data have not yet been analyzed, there have been no reports of major adverse social harms related to the research.

Conclusion: It is important to use a systematic approach to protecting participants in research using alternative designs with stigmatized populations.

Recommendation: Future research using alternative designs with stigmatized populations should consider using this approach to assessing its ethical appropriateness as well as developing and implementing Participant Safety Plans. In addition, future work should be directed at assessing this approach and creating materials and mechanisms to facilitate its use.

4. A quantitative framework for balancing ethical tradeoffs in vaccine study design during highly fatal, emerging infectious disease epidemics

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Policy issue: The deadliness of the West African Ebola epidemic stimulated debate on the comparative ethics of various study designs for phase III vaccine efficacy trials. Energetic debate focused on the conflict between the scientific and societal aims of research and the welfare of individual trial participants. One camp emphasized that rigorous identification of safe and efficacious vaccines could be crucially valuable for epidemic control. Individually randomized controlled trials (RCTs) are the fastest, most rigorous study design to evaluate safety and efficacy^{1,2} because they are statistically efficient and tend to avoid confounding bias, particularly when combined with blinding. Others, however, argued that withholding a promising experimental intervention from control participants at high risk of infection and death may fail to satisfy the principle of clinical equipoise³—originally defined as genuine uncertainty in the medical community regarding whether a participant would be better off in one trial arm versus another.⁴ These concerns led to proposals for non-traditional trial designs, including a ring vaccination trial, the use of delayed vaccination instead of control arms, and a stepped-wedge cluster trial (not implemented).^{5,6}

The a priori scientific value of a trial is traditionally quantitated by estimating its power, speed and rigor; these metrics of informativity, in part, determine a trial's social value. In contrast, no method exists to quantitatively characterize the ethical dilemma concerned with withholding interventions. The ability to quantitate only one side of the tradeoff between scientific value and participant welfare hampers discussions on how to balance the tension between them.

Commentary and recommendation: During the West African Ebola epidemic, some argued that it was ethically problematic to withhold experimental interventions from control arm subjects. Others argued that experimental interventions cannot be presumed efficacious *a priori* and must be rigorously tested before widespread rollout. Our quantitative framework unifies these two seemingly disparate perspectives regarding vaccine evaluation in the face of a deadly epidemic. We link each perspective to a different component of clinical equipoise and provide a practical framework for balancing these perspectives when designing trials. This framework uses Bayesian prior distributions to show that, within certain highly fatal disease contexts, conceiving of efficacy trials as having the dual goals of intervention evaluation and deployment is not akin to committing therapeutic misconception. This is because high disease severity and infection risk can lead to an intervention being probabilistically beneficial *a priori*, even under conservative assumptions about its anticipated promise. We focus on vaccines and not therapeutics for two reasons. First, vaccines have a greater history of success within efficacy trials, making probabilistic beneficiality more likely. Second, partially predictable variation in infection risk provides an opportunity for investigators to make explicit design choices that balance the goals of evaluation and rollout.

Determining a desirable balance between these goals can be achieved using quantitative metrics that measure each of them respectively. We use traditional metrics of evaluation (power, speed, rigor) to measure a trial's informativity. To measure the extent to which a trial withholds a probabilistically beneficial intervention, we define new metric of participant *risk spent* on information (i.e. avertable risk that is not averted in order to acquire information), by estimating the difference between each participant's outcomes in a proposed trial and an idealized scenario in which investigators allocate their available resources towards the sole goal of optimizing the sum of all participants' outcomes (for the condition under study). This idealized scenario is a useful reference point from which to examine alternative designs; it is not necessarily a goal in itself.

We advocate appropriately detailed simulation models to help understand how certain design modifications can pragmatically balance between these goals in the specific epidemic and logistical context. These include modifications that affect the speed with which a trial will detect an efficacious vaccine (sample size, enrollment rate, interim analyses, or risk-prioritized vaccination rollout) and those that systematically limit the risk spent by unvaccinated individuals (a delayed vaccine comparator arm or presumptive vaccination of subjects above a risk threshold). We provide illustrative simulation examples to highlight how some design modifications from a traditional RCT design allow for conscientious balance along this tradeoff.

This framework is not intended to replace other considerations regarding informed consent, community engagement, logistics or resource availability. Rather, this framework aims to complement those considerations in a way that allows various stakeholders to explicitly discuss how they would like to balance the risk spent by trial participants with trial outcomes that may provide societal value for others. Our approach is not prescriptive. We do not recommend a specific balance between these views as the single most ethical. Rather, we advocate this conceptual approach as a means of crystallizing the tensions between opposing viewpoints and facilitating transparent discussion to aid ethical and efficient responses to future emerging epidemics.

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5. Reconciling controversies over study design during Ebola and international harmonisation of regulatory requirements: a work package for the EDCTP

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Context

As the GFBR Background paper describes, the Ebola outbreak of 2014/15 saw the international community struggle with questions of methodology in the context of having no standard medical treatments available and of having several candidate medicines only just becoming ready to ‘test’ in humans for the first time. Radically different methods were proposed, mainly by past colonial partners for different reasons, and used during the outbreak with mixed and sometimes arguable results.

Current controversies

Priority is still given to Randomised Controlled Trials (RCTs) as a method of gathering clinical evidence during infectious disease outbreaks in terms of both speed and effectiveness (US National Academies, 12th April 2017), yet the FDA accepts that in some cases new medicines can be licensed for human use without any clinical evidence if it were deemed unethical to conduct clinical trials period (Edwards 2015). In 2012 for example, the drug levofloxacin was approved by the Food and Drug Administration (FDA) for plague caused by *Yersinia pestis*. Efficacy was extrapolated from an African green monkey model of pneumonic plague. Levofloxacin had previously been approved for other respiratory infections (i.e. nosocomial and community-acquired pneumonias), yet the licence for use in pneumonic plague was based solely on efficacy data from the animal model (FDA, 2012). If caught early, bubonic plague could be treated, thus making the threat of an outbreak of pneumonic plague a remote possibility. With such a regulatory precedent in mind and, despite important differences between Levofloxacin and candidate drugs for Ebola, it might seem strange why none of these candidates were not similarly licensed for general use on the basis of animal data alone given the real urgency and population need (albeit subject to inevitable delays in manufacture and distribution). In any case, by the time the candidate treatments were ready for human use, there were epidemiological data emerging from the field, which showed that there was variation in the accumulating case fatality rates from 50% to 80% between individuals and between reporting treatment centres (mainly MSF run facilities) such as they were early on. On this basis, the FDA concluded that sound science required a concurrent control (of best available supportive care) to reduce an anticipated bias associated with using historic controls (Cox et al. 2014). Variation between centres, they argued, also ruled out randomised trials at the cluster level including any step-wedge approach. Establishing causal relationships between treatment and clinical effect was their primary concern.

WHO, by contrast, recommended the compassionate use of convalescent plasma whilst observing any emerging aggregate outcomes (newly coined monitored emergency use of unregistered and experimental intervention MEURI). Single arm studies of this sort are subject to multiple biases (Rid and Emanuel 2015) so, in this case, policy placed the importance of gathering scientifically viable data as secondary to treating the interests of individuals with a therapeutic intent. The Ad hoc Ethics Group on Study Design, convened in September of 2014, accepted the use of alternative designs in principle without commenting further, apparently taking a more pragmatic stance (Calain 2016).

Proposed approach

The values at play here seem, at first sight, to be diametrically opposed, i.e. science first versus individual patient first, science second. However, from one direction, there is more work to be done on the relatively neglected scientific value of evidence of mechanisms (often derived from ‘in vitro’ laboratory research), the reach and relevance of multiple factors affecting extrapolation (over which there is no common understanding especially from animal data), and big datasets, as well as the epistemic advantages of mixed methods in clinical trials and so called triangulation of results. In the absence of ideal placebo controlled RCT data, we need a framework that sees researchers and regulators as able to draw on other types of evidence (e.g. animal trial data alongside, mechanisms, observational data, natural experiments). This should eliminate enough uncertainties and build a strong enough causal picture of the investigational therapy in order to ensure patient safety to a near (if not same) standard as would be sought using RCT data. From the other direction, it would be difficult to sustain a case for individual rights to try experimental treatments especially the more uncertain their effects or in the context of a public health emergency. And acceptable limits to exploitation by curtaining patient’s options and restricting access to experimental treatments for scientific purpose through RCTs are yet to be established. Yet both sides must be prepared to become better coordinated and even collaborate as another outbreak is highly likely.

We have recently secured funding from the EDCTP to facilitate regulatory work on morality in research study design and identifying the relative trade-offs implied by them, from the placebo controlled RCTs through to MEURI. As a result, the programme of work in PANDORA ID NET will have international reach and significance but has particular relevance to West African ethics committees and regulators. Having identified the trade-offs with each alternative design (using scenarios and standard gamble techniques for eliciting values), over the coming three years, we plan to engage in a process of communicative reason with African regulators and ethics committees with a view to ‘harmonising’ an approach to methodology during public health emergencies.

1. Procedure of deliberative communication through series of workshops
2. Limit ‘distortions’ of deliberation related to imbalances of political power and market failures for example
3. Convene a consensus summit with African Union planned for 2020
4. Revisit guidance issued by the International Conference on Harmonisation to encourage the Africa Union to participate as equal partners

The Global Forum for Bioethics Research presents a unique opportunity to initiate the process of communicative reason with, and to solicit values from, a much larger pool of those involved in the regulation and ethics review of research internationally.

6. Journeying through the development of a consensus-driven adaptive designs reporting guidance

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Introduction

The need to evaluate new health interventions using efficient trial designs has increased in recent years. Adaptive designs are one way to enhance study design efficiency. Adaptive designs offer the opportunity to use accruing data within an ongoing trial to modify, or adapt, aspects of that trial while preserving trial integrity and validity.

Although adaptive designs appear to offer many advantages, they are not routinely applied due to a number of obstacles that include: lack of practical knowledge; limited access to case studies to learn from; concerns about credibility and potential introduction of bias.¹⁻⁴

Adequate transparent reporting is one of the leading facilitators to address these obstacles. There is no existing reporting guidance tailored for trials that use adaptive designs.^{1,5,6} As a result, deficiencies in their reporting may influence their credibility and limit their ability to inform future related research.^{6,7} This work aims to address reporting deficiencies to mitigate some of the obstacles to the use of adaptive designs.

Methods

We formed a multidisciplinary international consortium of key stakeholders in clinical trials research to lead the development of a consensus-driven reporting guidance for trials that use adaptive designs in the form of a CONSORT Extension (<https://goo.gl/OF2q14>). As part of the Adaptive designs CONSORT Extension (ACE) project, we conducted a scoping review of the literature and held a face-to-face meeting on 17th January to initiate the development process. We are now surveying international stakeholders on their perception of the importance of potential reporting items during a Delphi process (2 to 3 rounds of sequential surveys from June to September 2017). A consensus meeting on the 8th November 2017 to reach an agreement on the content of the reporting checklist follows this. Detailed protocol is publicly accessible (<https://goo.gl/Ho747H>).

Results

We will talk about the underlying problems the ACE project aims to address, the development process of the reporting guidance, and share results from the Delphi process rounds and the consensus meeting. We will also discuss the lessons learned, and describe the future direction of the project.

Discussion

We hope this international CONSORT Extension guidance will mitigate some of the obstacles to the use of adaptive designs by enhancing their credibility and helping to improve their reproducibility and replicability through better and more transparent reporting. More so, help researchers design better adaptive trials to address research questions and bridge the gap in practical knowledge.

Funders

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- o Medical Research Council (MRC) Hubs for Trials Methodology Research (HTMR)

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7. Implementation of CRP point of care testing in primary care to improve antibiotic targeting in febrile and respiratory illness (ICAT)

Rachel Greer, Mahidol-Oxford Tropical Medicine Research Unit, Thailand

Brief description of the research project

We are designing a study to capture the normal prescribing practices and the impact of CRP point of care tests on antibiotic prescribing in Primary Care Units (PCUs) in two sub-districts in Chiang Rai province, Northern Thailand. The study will last 1 year.

The CRP tests will be available for use by routine healthcare workers (HCWs) on site, for patients presenting with a fever, history of fever or an acute respiratory tract infection (estimated 60,000 patients). A finger prick blood sample is required. Patients' autonomy will be respected and this test can be declined.

The impact will be monitored through routine electronic health records. Data collection will include the patient's number, age, sex, date of visit, PCU attended, chief complaint, observations (eg temperature), CRP result if applicable, diagnosis, prescription and referral status.

Background - relevant facts about the host country/community and disease studied

Antimicrobial resistance (AMR) is of increasing worldwide concern, with resistance developing to many common healthcare associated and community-acquired infections such as pneumonia. WHO describe AMR as a 'burgeoning and often neglected problem' in the South-East Asia Region.¹

Better targeting of antibiotics needs to start with simple tools to identify those patients requiring antibiotic treatment. C-reactive protein (CRP), a biomarker of infection, has been used for decades in high income settings to guide this decision. A 2014 Cochrane review concluded that CRP was the best available biomarker to guide the use of antibiotics in acute respiratory infections (ARIs).² A recent Vietnamese clinical trial showed that CRP testing could safely reduce antibiotics in patients with ARIs in primary care.³ We have just finished a clinical trial exploring CRP testing in fevers in Thailand and Myanmar with the interim analysis indicating similarly positive results (ClinicalTrials.gov Identifier: NCT02758821).

All these studies, however, are conducted in a research oriented context. What is most needed now is a pragmatic study of CRP testing in routine care, using simple point of care tests suitable for use in low level facilities by relatively unskilled personnel.

Chiang Rai province is the most northern province in Thailand. It shares borders with Myanmar and Laos. The population was estimated to be 1,157,302 in the Thai 2010 census.⁴ 32 PCUs serve the population of Chiang Rai town district. The PCUs are a vital part of Thailand's Universal Health Coverage, a nominal charge of 30THB is applied to each visit. They are routinely staffed by nurses and public health officers.

Ethical issues

Study Design

What are the advantages and disadvantages of a stepped wedge design?

(Individual randomisation would be inappropriate because the HCWs would be exposed to the intervention and this may impact their prescribing in the control group).

Advantages of stepped wedge design

Ethical

- All sites will benefit from the intervention; more socially acceptable. Local HCW are keen to use the CRP tests.
- Less equipoise required.

Resources

- Require fewer trainers/study staff.
- Can have fewer cluster sites (with more participants), may be beneficial if sites are expensive or limited. One of the main costs will be the CRP reader for each intervention site.

Analysis

- The same sites will act as your control and intervention sites, may give the study a higher power.
- Temporal changes can be modelled for, may be easier than accounting for heterogeneity between clusters in a cRCT (cluster randomised controlled trial). Prescribing practices vary greatly across the PCUs, they also serve different populations.
- May have fewer confounding factors.

Practical

- Reduce the risk of contamination (high turnover of staff between PCUs, may have been exposed to the intervention then move to a control site).
- Gradual introduction can allow for teething problems/changes to be made.
- May be easier to enrol PCUs and HCWs and keep them engaged throughout the study period as they will all receive the intervention at some point.
- Reduce logistical challenges of introducing the intervention to multiple clusters simultaneously. Furthest PCU is 2 hours away.

Against stepped wedge design

- Can take longer than a cRCT and have more drop out (depends if cross-sectional or multiple time points from the same participant).
- If there is policy change during the study period it will be harder to allow for its impact.
- If ineffective in the final analysis hard to justify cost, time, ethics of exposing all clusters to the intervention.
- Reporting and analysis is not well established (unlike cRCT).

Which design would generate the best evidence for policy change?

Reviews of implementation are often carried out using a stepped wedge or before and after study designs. Stepped wedge trials allow for a more thorough evaluation of the intervention.

Stepped wedge trials introduce the intervention to all sites, so may reveal differences in heterogeneous PCUs. Could help identify challenges to further roll out.

Should studies be carried out if positive results are unlikely to be incorporated into national health guidelines (due to budget constraints, other priorities etc.)?

- Difficult to justify the costs of the trial and potential risks to participants if it is unlikely to be adopted.
- However trials are needed to generate evidence for implementation and to assess the cost effectiveness of interventions before policy can be changed
- How much evidence is required to change health policy? How should this be produced?

How should investigators engage with the community, healthcare workers and health authorities to plan such studies?

- Interviews; high satisfaction among patients and local HCWs in our recent study of CRP POCT
- Collaborating; local health leaders are keen to use the CRP test. Although the test is not perfect they feel it is a significant improvement on current practice
- Meetings; the Thai FDA are supportive of the concept but need more evidence to change policy

Commentary on the issues, conclusions and/or recommendations for discussion or future research

Would you use a stepped wedge study design for this implementation study?

Will it generate the right evidence for policy change?

How should investigators engage with the community, frontline HCWs, senior HCWs, local and national health authorities to plan such studies?

When do we have enough evidence to move from research into implementation and policy change?

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“Pecha Kucha” Presentations

“Pecha Kucha” translates from Japanese roughly as “chit-chat”. Pecha Kucha presentations are designed to be delivered quickly and concisely, with slides **automatically** advancing every 20 seconds. They are an informal opportunity for GFBR participants to find out about each other’s research, viewpoints and experience.

The format does not allow for questions at the end of each presentation but you are welcome to discuss the presentations after the session or during breaks.

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

1. Alternative clinical trial designs for research on hypertensive disorders of pregnancy in low resource settings

Shivaprasad Goudar, KLE University's Jawaharlal Nehru Medical College

Hypertensive disorders of pregnancy are among the major contributors of maternal mortality and morbidity. Early identification, prompt referral and timely management at appropriate referral facilities can significantly reduce the burden of maternal mortality and morbidity. We recently completed a community based cluster randomized trial of a “Community Level Intervention for Pre-Eclampsia” (CLIP) package that involved task shifting of blood pressure monitoring during pregnancy to community health workers. Community health workers were trained for monitoring blood pressure with a novel semi-automated device during pregnancy and using a mobile based application (Piers on Move – POM) for guiding referral and treatment to a higher facility. The CLIP Trial hypothesized that implementing a community level evidence based care will reduce by 20% or more the pre-eclampsia related maternal and perinatal mortality and major morbidity by addressing ‘three delays’ in triage, transport and treatment. This Cluster RCT was conducted in Belagavi and Bagalkote Districts in Karnataka State, India; Ogun state, Nigeria; Maputo and Gaza Province, Mozambique; and Hyderabad and Matiari districts in Sindh Province of Pakistan.

An ongoing multicenter trial using a step-wedge design is testing the introduction of a novel vital sign alert blood pressure monitoring device in community settings for early identification and referral of pregnant women developing hypertensive disorders. Specifically, the trial is assessing whether implementation of a novel semi-automated vital-sign alert device and simple education package used by healthcare providers (HCPs) at community and facility levels will reduce maternal mortality and major morbidity from the three leading causes of maternal death worldwide (obstetric haemorrhage, sepsis and pre-eclampsia), in low-income country (LIC) populations. The trial is being implemented in India, Zimbabwe, Zambia (x2 areas), Sierra Leone, Uganda (x2 areas), Haiti, Malawi, and Ethiopia.

The presentation will address the challenges of implementing these two trials and the ethical issues associated with them.

2. A quantitative framework for balancing ethical tradeoffs in vaccine study design during highly fatal, emerging infectious disease epidemics [see Poster Summaries for a fuller description]

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During emerging epidemics, rapid development and testing of new vaccines may be critical to curbing transmission and saving lives. However, vaccine efficacy trials in such contexts may face considerable logistical, epidemiological, or ethical impediments. During the 2014-2016 Ebola virus epidemic, there was vigorous debate on the tradeoff between a trial's ability to yield information of scientific and societal value versus the perceived ethical dilemma of withholding potentially life-saving vaccines from control participants. Whereas the scientific value of a trial is often estimated in terms of statistical power, speed, and rigor, we lack similar metrics for the ethical costs of withholding interventions. Here, we introduce a conceptual framework that fills this gap. We show that even untested vaccines against severe diseases may be probabilistically beneficial—i.e. after accounting for realistic uncertainty, trial participants are expected to be better off vaccinated than not. While accounting for this uncertainty, we compare estimated trial participant risk under a hypothetical, idealized vaccine rollout scenario to that under various candidate trial designs, in order to elucidate specific quantitative tradeoffs between cumulative risk to trial participants and information gained. Through an illustrative example, we highlight specific trial-design modifications that allow for conscientious balance between minimizing participant risk and acquiring information of societal value. These include modifications that affect the speed with which a trial would detect an efficacious vaccine (greater sample size or enrollment rate, interim analyses, or risk-prioritized vaccine rollout), which leads to earlier vaccination of control participants should the vaccine be efficacious, and those that systematically limit the risk “spent” by unvaccinated individuals (e.g., delayed vaccination of controls, or presumptive vaccination of subjects above a risk threshold). We advocate this conceptual approach as a means of clarifying tensions between opposing viewpoints and facilitating transparent discussion to aid ethical and efficient responses to future emerging epidemics.

3. Ethical issues of alternative clinical trial designs and methods in Myanmar

Khine Zaw Oo, Defence Services Medical Research Centre, Myanmar

Many local and international researches were being done in Myanmar for decades. Most of them are cross-sectional descriptive studies with only a few phase III clinical trials. Number of Research Ethics Committees has been rising at universities and research institutes and two RECs became internationally recognized recently.

As cost of therapy development cannot be recovered from sales, multicenter alternative designs are done. There are only a few researches using alternative design in Myanmar yet. Alternative research design is used in rare diseases, most of which are of genetic origin and hence children are involved. The others

with psychiatric conditions. Researchers and RECs are not familiar with these designs. Sometimes, high dose effect can occur if the two treatments are compared sequentially in single subject. Again, effect cannot be seen easily if new therapy has prolong and irreversible effects and if the disease is not stable.

Along with other research designs, alternative designs face with limited information about new therapy and withdrawal of treatment in placebo group. In cross-over trial design, subject retention is a problem but it is not so much in LMICs.

There is no ethical issue yet but RECs have to prepare to ensure there is no coercion of affected children and other vulnerable group, physical risk in cross-over trial design and in placebo group, justice for the host country as research will be done more in LMIC countries, scientific validity and beneficence.

4. Alternate to clinical trial design for Ayurveda in chronic non-communicable diseases, in non-emergency settings

Vina Vaswani, Yenepoya University Mangalore, India

For many chronic non-communicable diseases, the Indian people are once again looking to Ayurveda, a complementary and alternative systems of medicine (CAM), that enjoys a wide, unregulated practice base. The crises in cost, confidence and conscience in allopathy have caused the shift to CAM (Bhatt 2001). The use of formulations in Ayurvedic practice requires generation of high quality evidence (Sivaramakrishnan, 2016). In reality, evidence-based practice on Ayurvedic formulations has been mostly anecdotal and to get them in the mainstream to be accepted as treatment needs the backing of clinical trials. Various combinations of the four main non-hierarchical facets for treatment in Ayurveda – Tradition (inherited from ancestors), Convention (from other examples), Belief (the formula of dravya, guna, virya and karma), and Evidence Based Medicine – are needed to personalize patient care (Panda 2012).

The present randomized clinical trial (RCT) designs rely solely on measurable, hard outcomes. Do these RCT designs get to capture the complex interventions of CAM? (Walach et al 2006). Clinical medicine in Ayurveda addresses the imbalance in the body homeostasis (doshas). No two patients are treated the same. Hence the assumption of one-size-fits-all that underpins clinical research designs may not be useful in Ayurveda.

Every research method has a strength and weakness which cannot be resolved within that method. The method of studying the therapeutic effect independent of context is flawed. Triangulating results achieved by several different methods, such as the one proposed by Walach et al (2006) may be a better approach to evidence-based Ayurveda, than RCT alone. In addition, retrospective audits of well documented data, case studies and case series with outcomes can add valuable information.

Circular design of research methods involving different methods ensures complementarity, synergistically enhancing the power of the study, by combining efficacy outcomes with narratives on real-life experiences.

“The essence of circularity is the ability to see the whole problem with patient centered and human therapeutic perspective allowing rigorous evidence, individualized decision-making at the clinical interface.” (Walach et al 2006)

5. Paving the way: Better understanding of the Egyptian research ethics committees, and regulatory authority for alternative clinical trial designs

Hany Sleem, National Hepatology and Tropical Medicine Research Institute, Egypt

Research ethics committees (RECs) and regulatory authority members' proper training are very important for correct gate keeper function. In Egypt, more than 50 RECs are present; 40 of them are members of Egyptian Network of Research Ethics Committees (ENREC) which was created in 2008 to raise the harmonization between RECs. The Egyptian regulatory authority for reviewing of clinical trial and approving new drugs is composed of three bodies; the Central Directorate of Research and Health Development, National Organization for Drug & Control Research and National Organization for Research & Control of Biologicals.

Alternative clinical trial designs are not common practice in Egyptian clinical trials. Only one Adaptive trial for a new drug was submitted for review to the Egyptian regulatory authority last year. But as Egypt is a developing country it is prone to infectious outbreaks or natural disaster thus it will be candidate to alternative clinical trial. At that time RECs and regulatory authority must be on standby for ethical decisions based on enough scientific and ethical understanding of these new types of clinical trial.

Until now, there is no special training or awareness sessions for Egyptian regulatory authority, RECs, or community members on this topic. Therefore, a series of 30 min presentations followed by 1 hour of discussions targeting the next ENREC meeting and the three components of the Egyptian regulatory authority will be held. These presentations are based on GfBR 2017 Background paper, European Medicines Agency (2007) and Food and Drug Administration (2010) guidelines. Discussions will focus on the ethical dilemmas of Alternative clinical trial designs and their suitability to the Egyptian culture and regulations and this programme will be supported by ENREC.

6. Ethics of alternative clinical trial methods in LMIC research: The Gambia Hepatitis Intervention Study experience (GHIS)

Gibril Ndow, Imperial College London/MRC Unit The Gambia

Background

The Gambia Hepatitis Intervention Study (GHIS), initiated in July 1986, is a three-phase collaborative project by the International Agency for Research on Cancer (IARC), The Gambia Government, and the MRC Unit The Gambia. The study was set up to evaluate the protection conferred by infant HBV vaccination against infection, chronic carriage, and hepatocellular carcinoma (HCC). Using a stepped-wedge design, the trial randomly phased HBV vaccine into the Gambian Expanded Program on Immunization (EPI) over a four-year period recruiting 124,577 children randomized to receive the existing EPI vaccines or the EPI plus HBV vaccines. A National Cancer Registry was set up for active HCC surveillance, and all HCC cases of appropriate age would be matched against the GHIS database to determine HBV vaccination status.

Ethical considerations / issues

Logistics, cost and availability of vaccine in the 1980s favoured a stepped-wedge design with minimal ethical issues over its implementation. In addition, there was a unique opportunity to quantify the precise benefit of vaccination against HCC without the need to delay mass vaccination by decades. However, with the final outcome of the trial not measurable until after 30–35 years, important concerns were raised: (1) It was possible that during the follow-up period, a more effective vaccine could replace the trial vaccine in EPI programs, making findings obsolete; (2) unless the net benefit of vaccination against HCC was modest, this will become apparent from regions with uncontrolled vaccination programs; (3) HBV vaccination would be adopted by most nations and findings of efficacy, or lack of, against HCC would not have much impact on practice and policy. Consequently, the four-year delay in rolling out of the HBV vaccine to certain groups in this study could be deemed unnecessary and arguably unethical, given that (at the time of the study) the vaccine was already shown to be effective against acute infection and hepatitis B surface antigen carriage.

GFBR fellowships

The GFBR fellowships provide a unique opportunity for people attending the GFBR meeting to work in partnership to further explore issues that have arisen during the course of a GFBR meeting. There are three types of fellowship:

Travel fellowships support visits to a country other than the country where the applicant is based. They are designed to give the applicant the time needed to develop a topic and also learn from being in a different research environment. The length of the visit is usually between 2 weeks and 3 months. The scheme is not designed to support travel from one high income country to another.

Project fellowships support specific projects, the outputs of which may be conference presentations, academic papers etc. It is expected that any academic outputs are not sole-authored pieces or collaborations solely with others from the fellow's current institution.

Meeting fellowships support the costs of holding an event that builds on the annual GFBR meeting discussion.

General conditions

The following conditions apply to all three fellowships:

- Applications are only open to people who attended the 2017 GFBR meeting.
- Applications should fit in with the goals of the GFBR and promote new global South/South or North/South collaborations.
- Applications should be relevant to the subject matter of the GFBR meeting (i.e. ethics of alternative clinical trial designs and methods in LMIC research).
- The normal maximum that can be applied for is US\$10,000 but a higher amount will be considered in exceptional circumstances if there is a strong justification. Applicants should not automatically request the full normal maximum.
- Applications for conference attendance as a stand-alone activity will not be considered.
- Only one application per fellow is permitted.

The third round of applications will be launched at the GFBR meeting. Please see the GFBR website for further guidance on how to apply.

Potential hosts for GFBR fellows

This year we have identified a number of potential hosts, many of whom are attending the meeting. If you have an idea for a fellowship and would like to explore whether it is a good fit with the host institution, please do make contact either during or after the meeting:

1. Ethox Centre, Nuffield Department of Population Health, Oxford
Contacts: Mike Parker (attending GFBR)
E: admin@ethox.ox.ac.uk
2. South African Ethics Training Initiative (SARETI), University of Kwazulu-Natal
Contact: Doug Wassenaar
E: wassenaar@ukzn.ac.za
3. Mahidol Oxford Tropical Medicine Research Unit, Thailand
Contact: Phaik Yeong Cheah (attending GFBR)
E: Phaikyeong@tropmedres.ac
4. Facultad Latinoamericana de Ciencias Sociales
Contact: Florencia Luna (attending GFBR)
E: lunitaviajera@yahoo.com.ar
5. Regional Program on Bioethics, Pan American Health Organisation
Contact: Carla Saenz (attending GFBR)
E: saenzcar@paho.org
6. Centre for Biomedical Ethics, National University of Singapore
Contact: Teck Chuan Voo (attending GFBR)
E: teck_chuan_voo@nuhs.edu.sg
7. Institute on Ethics and Policy for Innovation, McMaster University
Contact: Claudia Emmerson
E: emersoc@mcmaster.ca

The Institute on Ethics & Policy for Innovation (IEPI) at McMaster University, Canada, invites GFBR Fellows to join us in 2018. IEPI is focussed on identifying, understanding, and addressing ethical challenges and policy gaps in global health research. Our goal is to integrate ethical thinking into the innovation pathway for technologies and interventions with the potential to improve and save lives, to support their discovery, development, and ultimately their delivery to the people that need them. We are a multi-disciplinary team that works collaboratively with partners and stakeholders to develop culturally respectful ethical solutions. Our work addresses a spectrum of issues, but we are especially interested in ethical issues related to: i) data governance and data sharing; ii) clinical trials in low resource settings; iii) management, control, elimination and eradication of infectious disease; iv) gender, and the inclusion of women and girls in global health research. IEPI delivers the ethics consultation and research program for the Bill & Melinda Gates Foundation. Interested GFBR Fellows are invited to contact Dr. Claudia Emerson: emerson@mcmaster.ca to discuss potential projects for 2018.

For more information, please visit: www.iepi.mcmaster.ca, and Discover Hamilton #secretsout <https://www.youtube.com/user/HamiltonTourism>

8. Rotman Institute of Philosophy, Western University
Contact: Charles Weijer (attending GFBR)
E: cweijer@uwo.ca

Charles is undertaking a project related to the meeting theme and welcomes a GFBR Fellow in 2018. For more information about the project, please see below, consult this website <http://www.rotman.uwo.ca/portfolio-items/pragmatic-rcts/> or contact Charles.

Project summary: Pragmatic RCTs provide patients, health providers and health system managers with reliable information on the safety, effectiveness and cost of treatments. Although ethical guidelines exist to protect participants in research, they were not written with pragmatic RCTs in mind. The lack of fit between current guidance and pragmatic RCTs leads to inadequate protections and unnecessary obstacles. Our research team, comprising 25 philosophers, trialists and biostatisticians from five countries, will develop guidance for the ethical design and conduct of pragmatic RCTs. Questions addressed include: When stepped wedge RCTs seek to study the roll-out of government policies, ought they be considered research or program evaluation? When pragmatic RCTs compare routinely available medical treatments, should the study interventions be classified as research or practice? Must patients in pragmatic RCTs always be informed about trial participation and provide informed consent? We will address these (and other) questions through a combination of ethical analysis and empirical study. This work will feed into a consensus process that will generate ethical guidance for researchers and research ethics committees globally.

We're very grateful to everyone who has offered to be a potential host!

If you are interested in hosting a fellow in 2018 please don't hesitate to get in touch with Adrienne (gfbr@wellcome.ac.uk).

Website and social media

Website

The GFBR website contains details of all previous GFBR meetings, including meeting reports and presentations where available. Presentations from this meeting will be posted on the site shortly after the event. www.gfbr.global

Social media

At this Forum meeting we encourage the use of social media to engage in conversation and to spread the discussions to those unable to attend the meeting itself.

If you use Twitter, please use the hashtag [#gfbr2017](#) to tag your tweets about the meeting.

Social media etiquette

Social media is still relatively new at a lot of academic conferences and meetings, so please follow these guidelines to ensure that it is used in a positive way that benefits the meeting and its participants:

1. Be polite and constructive

If you are going to tweet during a presentation or discussion, make sure you do so on a positive note. Share what you learned from the session or pose an interesting key question that would warrant further discussion. If the presenter has a social media profile, tag them in your post, and use the conference hashtag [#gfbr2017](#).

2. Respect presenters' requests for no social media

Some topics discussed may be sensitive or present early findings from research that has not yet been published. The chair should indicate at the beginning of a session if the presenter would prefer their talk not to be tweeted.

3. Engage with others

The meeting is an opportunity to learn from others, to hear about their experiences and perspectives. Social media is a useful tool for these interactions but do take the opportunity to talk to people in person during the breaks as well!