GFBR Accomplishment Report

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The GFBR Grant was used to organize a preconference workshop on Ethical Issues in Innovative Design. Representatives from various research stakeholders were invited as facilitators to present and lead the discussion of Asian case studies of innovative design. The scientific merits of the innovative designs were presented in the case studies while the group workshop of each case discussed the ethical issues together with the suggested measures on how they should be addressed.

FERCAP Pre-Conference Workshop Agenda
13:00-17:00, 18 November 2018
Venue: Linkou Changgung Memorial Hospital, Taoyuan, Taiwan

Facilitators:

	Name	Affiliation	Designation
1.	Phaikyeong Cheah	Global Forum for Bioethics in Research; Mahidol Oxford Research Unit	Scientist
2.	James Watson	Mahidol Oxford Research Unit	Scientist
3.	Srisin Khusmith	Institute of Tropical Medicine, Mahidol University	Scientist, Research Ethics Committee Member
4.	Cristina E. Torres	FERCAP	Social Scientist, Research Ethics Committee Specialist,
5.	Jan Helge	Oslo University	Bioethicist

Participants: REC members and investigators

Training on ethical issues of innovative alternative designs in health research

- Step Wedged Cluster Randomized Trial (SWCRT) in Public Health
- Adaptive Platform Trial
- Use of Controlled Human Infection Models

Objectives:

- To discuss case studies that make use of innovative/alternative designs in health research
- To discuss the ethical issues in innovative designs
- To support participants from LMICs to participate in the workshop
- To develop common approaches in the review of innovative design in health research in Asia-Pacific

AGENDA

13:00-13:30	**Introduction to the Use of Novel/Alternative Design in Health Research**
13:30-14:00	**Use of Cluster Randomized Trial Design** **Case study 1:** Community-directed educational intervention for malaria elimination in Bhutan
14:00-14:30	**Adaptive Design** **Case study 2:** Ascending dose primaquine regimen for the radical cure of vivax malaria in G6PD deficiency
14:30-15:00	**Human Infection Model** **Case study 3:** Clinical Trial of an Oral Live *Shigella sonnei* Vaccine Candidate, WRSS1, in Thai Adults
15:00-16:00	**Group Discussion: Ethical Issues in Innovative Design**
16:00-17:00	**Group Reports**
17:00-17:30	**Synthesis**

Workshop Outcomes:

1. The 3 case studies chosen were done in Asia and received ethics approval in the region. The workshop familiarized the REC participants with innovative designs currently used by researchers in Asia to enable them to analyze the ethical issues involved.
2. It provided an opportunity for a dialogue between the scientists and REC members with the scientists highlighting the scientific advantages of 3 types of innovative design while the workshop participants deliberated on the ethical issues involved in innovative design and how they should be addressed.
3. Ethical issues related to possible risks were identified during the workshops:
   A. Adaptive Design
      a. The protocol has social value since G6PD patients do not react well to primaquine but burden of disease should be determined among the target study group
      b. Risk mitigation measures should be in place in the adaptive design protocol. To be prepared for possible hemolysis, the hospital blood bank will be informed of the blood-type of the healthy volunteers and corresponding blood will be set aside for the duration of the trial. A 24-hour emergency medical service will be available from the hospital.
      c. Multiple one-to-one sessions in Thai language explaining the possible risks of trial participation will be done. Only those who fully consented will be enrolled.
      d. Recruitment procedures should be explained in the protocol and informed consent forms should contain comprehensive information
      e. Given the possible changes in the protocol, there should be an efficient way of communicating changes to individual participants.

   B. Human Infection Model

      a. Scientific issues: It is important to establish the burden of disease in disease endemic areas to justify the use of the human infection model on healthy individuals. The scientific merits of the protocol should also be determined to justify the risks involved. that study

objectives are achieved. It should also be checked if an alternative intervention is already available. WHO recommends that scientific and ethical experts should be involved in the review of CHIMS protocols.

b. Risk determination (e.g. clinical related risks of a vaccine trial, possible infection, etc.) and mitigation measures (access to care, etc.) should be defined in the protocol and the consent forms that should be closely examined by the research ethics committee.
c. The benefit of the research is largely for the public health sector in terms of the knowledge gained for better disease prevention measures. Benefits should also be maximized by sharing study results with the scientific community and areas where epidemic occurs.
d. Informed consent procedures should not be limited to individual participants and should include community and family consultations since individuals may possibly infect family and community members. Innovative consent information sheets should be developed for better communication with different types of stakeholders. The consent process in CHIMS protocols should be dynamic and continuing to allow for voluntary participation should additional risk findings are found. In community settings, community perception and cultural idiosyncracies should be examined to be able to adopt culturally sensitive measures in the conduct of the study.

C. Cluster randomized trial

It is a useful design for public health protocols, including the rollout of vaccines for disease prevention. The case that was used only had two groups/ clusters and was not a step-wedged study. Nevertheless, its advantage is being able to simultaneously do research and roll out of a program at the same time.

a. The ethical question is whether delayed roll-out of a public health program is justified. It has to be determined if clinical equipoise exists (when the policy maker does not know whether the intervention will work in a specific setting.) Conducting research during roll-out is capable of gathering evidence to prove the safety and efficacy of an intervention to justify its subsequent roll-out in other clusters. In a public health program, there should be evidence that the program/ intervention is good.
b. Should research come first before implementation of a new program? It was discussed that programs that have WHO guidelines already have evidence of good results. However, it is yet unsure if these programs would work in specific country/ community settings. Intervention done in one community/setting might not be applicable to others due to varying factors. Is it justified to do research and health care at the same time? It was explained that the cluster randomized design may be classified as operations research.
c. Is there any harm in doing health care delivery and research together or should it be sequential i.e. do research before rolling out? It was argued that this is the justification of step-wedged design. The PI/ implementers can do research about program implementation and provide necessary adjustment if they might identify some weaknesses during health care delivery. The researcher/ implementers can improve the program and then proceed to the next cluster. This becomes a learning experience.
d. Is there any roll-out happening in between modification of programs from one step to another? It was clarified that the program/ health care is simultaneously rolling out. The advantage of step-wedged is that it is site-specific. The problems identified

in the first group may be addressed in the next cluster where it is implemented. The roll out is about a specific public health program but procedures of implementation might vary depending on research outputs.

e. This design will initially involve one control and one intervention group. The researcher should determine the unit of analysis, e.g. a health cluster with individual participants. The cluster/ community is not necessarily a geographical area. In social science a community is defined as a group of people with the same interest or experience (e.g. patient group). Research results are grouped and analyzed according to cluster for comparison of similarities and differences. Pre and post intervention surveys are done in both arms to determine if desired changes have been achieved in the intervention arm. The sources of bias in the design should be examined, e.g. contamination between the intervention and control groups. Feasibility should be determined at the start to ensure that the research design is administratively and logistically possible to be done in groups/ clusters.
f. In this case study, the unit was the district. The community directed intervention was rolled out into two districts, one served as intervention while another district served as control for better comparison. If the intervention results are good, the researchers cross-over the interventions at post-trial. It was clarified that crossing over was done after the investigator provided evidence that the intervention was good and that the participants in the control group would benefit from the cross over. The cluster randomized design may be done in other settings such as hospitals or schools and ensuring homogeneity among clusters would account for better comparison. The roll-out is sequential since it is step-wedged and the program is constantly being improved.
g. How is comparability ensured? Demographic data and social indicators may be used and clusters may be classified into class of municipality, population size, mortality and morbidity rates, etc. Should there be reports on the first stage before proceeding to the next stage? It is advisable that assessment reports be made. The guidelines said that reports should be done at intervals, after each roll out or after each cycle.
h. What are the significant issues in LMICs that need to be addressed when using cluster RCT design? Getting authority from the gatekeeper serves the purpose of getting community/ cluster permission before protocol implementation. Then individual consent is taken from randomly chosen participants.
i. The research ethics committee should ensure that the research intervention is potentially beneficial to the cluster. Informed consent is first taken from the gatekeeper before initiation, then, from individual participants within each cluster. Is there a need to involve community gatekeepers? The gatekeeper is defined as someone who has legitimate authority in the cluster. This depends on the unit of analysis as stated in the protocol. A gatekeeper may be a formal (i.e political leader) or an informal leader (i.e leader of NGO, president of community groups/ societies). The gatekeeper is important in implementing policies that may be formulated from the public health research to be done. It is a standard procedure to go to the gatekeeper as indicated in the Ottawa statement. The involvement of gatekeepers and other community stakeholders would ensure sustainability and make the rollout easier.
j. How will cluster/ group consent be determined if there are dissenting opinions within the cluster/ community? Before the roll-out of the program/research, the cluster must decide on the criteria to arrive at a group decision to grant or deny permission

for the study. A community meeting may be convened to arrive at a decision and make recommendations on how individual/ household consent should be taken. What is the purpose of establishing the criteria on getting ICF when the intervention will push through even if there are dissenting opinions within the cluster? The minority should be given importance and their voices should be heard to serve as valuable inputs to improve program implementation.