# *Ethical issues related to study design for trials on therapeutics for Ebola Virus Disease*

***WHO Ethics Working Group Meeting***

***20-21 October***

***Summary of Discussion***



WHO/HIS/KER/GHE/14.2

Clinical trials of potential therapeutic agents for Ebola virus disease (EVD) are being considered in response to the Ebola epidemic in West Africa. A meeting of the Ethics Working Group was therefore convened on 20-21 October to map out the ethical issues relevant for such trials.

Ethical issues surrounding the possible use of unregistered preventive and therapeutic agents in the current Ebola outbreak were discussed during an Ethics Panel meeting on 11 August 2014 and an Ethics Working Group meeting on 3 September 2014. Discussions from these previous two ethics meetings inform this report.

A consensus was reached during the 11 August Panel discussion that provided certain conditions were met[1], (1) it would be acceptable to use promising (unregistered) experimental agents against EVD, (2) that the use of such agents should be scientifically studied, and (3) that further analysis of ethical issues specifically related to trial designs for the use/study of such agents was needed.

The most recent Ethics Working Group meeting on 20 and 21 October at WHO in Geneva brought together members of the WHO Ethics Working Group with statisticians, methodologists, drug regulators, researchers, ethics committee members and delegates from affected communities in West Africa, and representatives from other organizations responsible for providing care to those affected. The purpose of the meeting was to learn about possible clinical trial designs and to map out the issues to be considered by investigators, ethics committee members, decision makers and other stake-holders in developing ethically acceptable and scientifically sound studies which can be effectively implemented in West Africa for the evaluation of potential therapeutic agents for EVD. Recognizing that the ethical considerations for preventive vaccine trials in healthy and presumably uninfected individuals are different, the meeting focused its attention only on therapeutics and not on vaccines.

The primary objectives of the meeting were to:

- Conduct ethical analysis of the available study design options (e.g. with respect to risks, benefits, equity, autonomy, standards of care, etc.)
- Provide advice on the ethical considerations that are relevant for utilizing various study designs in particular contexts.

The Ethics Working Group was informed by discussions with the methodologists, trialists, an MSF representative, regulators and participants from West Africa.

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[1] http://www.who.int/csr/resources/publications/ebola/ethical-considerations/en/

This document summarizes areas where the Ethics Working Group members reached agreement, outlines some key points for consideration in undertaking trials, and offers a decision matrix for the use of researchers, research ethics committees and other stakeholders in considering whether proposed studies are ethically acceptable. More detailed discussion of the Working Group is available in a separate document.

**Areas of consensus of the Working Group:**

**Context Matters**

1. There is an ethical imperative to carry out research on potential therapeutic agents against EVD.
2. Even in the context of a public health emergency, unregistered and experimental drugs and therapeutics must be tested for safety and efficacy using rigorous methods and simple but properly designed clinical trials. In the context of the current Ebola epidemic in West Africa, WHO has already published recommendations that it is ethical to make investigational therapeutics available outside of clinical trials for "emergency use" provided clinical data from their use is systematically collected and shared. Such "emergency use" should not preclude or delay the initiation of more conclusive investigations of the intervention in properly designed clinical studies. The latter, if appropriately designed and executed, may yield generalizable conclusions that result in greater societal benefit.
3. The WHO Ebola Ethics Working Group proposed that the term "monitored emergency use of unregistered and experimental interventions (MEURI)" should be used in this case instead of "compassionate use" – a term that can have other meanings, such as use of an investigational intervention for patients outside of an ongoing clinical trial or the indicated scope of utilization.
4. The recipients of experimental interventions, locations of studies, and study design should be based on the aim to learn as much as possible, as quickly as possible, without compromising patient care, local community values or health worker safety. Trials should be designed and conducted with the active participation of local scientists and researchers, and with proper consultation with communities and local ethics committees.
5. In principle, so long as standard requirements for human research ethics are met, all scientifically recognized methodologies and study designs should be considered as ethically acceptable—whether they are placebo controlled randomized trials or trials that don't involve randomization to control groups. However, the reality at the sites where the research would be conducted should be taken into consideration. Research must be designed taking into account the scarcity of health care providers, possible availability or non-availability of additional research staff, the infrastructure and resources accessible at the health care facility, the patient load, etc.
6. Trialists need to consider not only what resources are available to allow for the proper conduct of the trial, but what resources need to be added in order to ensure

that patient care related activities/processes remain available to those attending the health care facility. Trials should not be done where they take away resources necessary for sustaining the health system locally.

7. The choice of study design is also contingent upon factors such as prior knowledge about safety/effectiveness of novel therapies in animals and humans; number of doses available; number of doses likely to become available (which raises issues of production scaling up, and continued access); ease of administration; additional support required (e.g. monitoring of clinical chemistry); ease of monitoring; risk to health care workers; etc.
8. Some trial designs may not be acceptable to the study population for various reasons, or not feasible at the study site for logistical reasons. Community engagement prior to and during the conduct of a trial is therefore an ethical requirement.
9. Real-time data collection and sharing is urgent--and obligatory--to ensure that potential therapeutic agents can be quickly evaluated and developed.

**Choice of study designs**

10. Methodologically, placebo controlled trials are considered by many to be the gold standard for conducting clinical trials for investigational drugs/therapeutics. Where the agents have an established safety record and preliminary efficacy data, including in predictive animal models, placebo controlled randomized trials may become less desirable. In the context of the current Ebola epidemic in West Africa--where the disease has a high fatality rate, and there are tensions between local communities, governments and healthcare workers--it may not be acceptable nor feasible to conduct randomized placebo controlled trials. Some members of the Working Group argued that in certain situations, it may also be unethical to do so. On the other hand, it was noted that conducting clinical trials without an appropriate control group could lead to uninterpretable or misleading trial results where it is not possible to tell if an investigational therapy is helping or hurting patients, and this might also be considered as potentially unethical. Participants from Guinea and Liberia, among other things, expressed their view that individually randomised placebo controlled trials would not be acceptable to local communities because such trials would deny a new experimental treatment to some participants.
11. Conducting individually randomized controlled trials with a control comparator (other than placebo) may not be acceptable to the local community if the control arm does not include a potential therapeutic intervention (even if it is not previously tested) beyond standard/supportive care;
12. In this context, an adaptive trial design that has the capacity to yield meaningful and interpretable data quickly in the midst of the (Ebola) epidemic might be considered as preferable. An adaptive design could include elements of randomized controlled trials, cluster randomization, stepped wedge, and single arm comparison trials. Adaptive trial designs are more complex to coordinate among sites. An adaptive trial

design can be utilized to evaluate patient outcomes beginning early in the clinical trial and the trial can be modified in accordance with those findings. Modifications may include dosage, sample size, targeted treatment group, treatment arms and patient selection criteria. In some cases, the trial can be an ongoing process that regularly adds and drops patient groups or treatment arms as more information is gained. The adaptive design will include the appropriate interim analyses and stopping rules including for significant efficacy, futility or safety.

13. Trials must undergo review by, and receive approval from, an appropriately appointed research ethics committee and must also be monitored by an appropriately constituted Data Safety Monitoring Board.
14. Cluster randomized trials with different clusters receiving different potential therapeutics are generally seen as acceptable ethically, methodologically and logistically. Randomization by cluster rather than by individual may be perceived as fair and more acceptable to the community. It may also achieve better compliance because each centre will eventually be able to provide a (more) active intervention. Compared with individually randomized trials, cluster randomized trials are more complex to design, require more participants to obtain equivalent statistical power, and require more complex analysis[2].
15. Stepped Wedge design is seen as having several advantages because it utilises randomization, and the staggered implementation of the intervention makes it more feasible to implement. The fact that all study communities/groups will eventually receive the active intervention being evaluated may also promote community acceptance.
16. A single arm non-comparative study using retrospective data from a non-randomised control group (for example collected from the literature, or from data currently being collected in the field) is often used in serious, life-threatening conditions, when the disease or condition to be treated has a well-documented, highly predictable course. Since all participants in such trials receive the same intervention they may achieve community acceptance and good compliance among subjects. While being simpler to run, this design has a high risk of bias and may lack internal validity. The results of single arm studies are most interpretable in cases where the effect of the study intervention is especially dramatic. Differences in patient outcomes derived from factors other than the investigational drug (e.g., patient factors, level of supportive care) make this a design that may lead to erroneous conclusions.

[2] **http://www.bmj.com/content/328/7441/702?fromsource=nelm**

**The community**

17. Currently there is no agreement in the medical community on the appropriate standard of care. Defining the appropriate standard of care and the effect of this on mortality is an important research priority.
18. Engagement with local communities is challenging but of paramount ethical importance in selecting study designs, and community acceptance is essential. Communities may not accept particular study designs for social, cultural, political or ethical reasons.
19. There is an urgent need to review existing anthropological research and to conduct further anthropological studies to learn more about effective ways of engaging local communities, particularly during epidemics.
20. Local research ethics committees must be offered appropriate support to ensure they have the capacity to provide the rigorous ethical review required for such protocols, particularly those study designs that are more complex and adaptive in nature or which involve vulnerable populations or those unable to give consent.

**The research participants**

21. Even though Ebola is a public health emergency, informed consent remains an important ethical requirement. However, consent processes must be adapted to contextual limitations. Innovative approaches may need to be considered to ensure comprehension and voluntariness. These could include video or audio recordings or, in some cases, surrogate consent.
22. It is ethically important to ensure that vulnerable populations such as pregnant women and those with diminished autonomy such as children or those with mental incapacities are not arbitrarily excluded from trials. Instead their inclusion into clinical trials should be guided by a risk benefit analysis and the ability to secure adequate consent.
23. It is ethically advisable to ensure adequate follow up of study participants until the study end point. Therefore study designs should be developed keeping in mind practicalities of following up patients in the existing complex socio-economic environment of the epidemic. Careful consideration must be given to the ability to draw on stretched resources in following up cases, ensuring privacy, storing, testing and processing samples and gathering follow-up data on them.

**Healthcare workers and researchers**

24. The choice of the therapeutic to be tested and the study design to be implemented must be guided by the principle of safety and reciprocity to all persons involved. The risk to health care workers or research staff posed by a study design or a study drug or intervention is a crucial consideration, and such risks should be minimised to the greatest possible degree. Study designs that are simple and therapeutics that are easy to administer are preferable to those that are likely to expose healthcare

workers or research staff to additional serious risks: e.g., those requiring multiple blood samples, intravenous fluids or blood products, prolonged exposure to infected patients, or more frequent monitoring.

25. Healthcare workers must be well informed about, and agree to be implementers of, the research; and, should they agree, they must be trained and provided adequate protective equipment and resources.

The matrix provided below takes into consideration many of the issues discussed above and could be useful for investigators, ethics committees, sponsors etc. when developing research studies.

| | **RCT** | **Stepped Wedge Design** | **RCT-SR** | **Cluster Randomized Trial** | **Comparative non-randomized with concurrent control** | **Single Arm Non-Comparative** |
|---|---|---|---|---|---|---|
| **Site related issues**<br>1. Healthcare provider availability<br>2. Research staff availability<br>3. Infrastructure<br>4. Capacity for ethics review | | | | | | |
| **Drug related issues**<br>1. Prior knowledge about safety/effectiveness<br>2. Number of doses available<br>3. Number of doses likely to be available/scaling up issues/continued access<br>4. Ease of administration<br>5. Additional support required e.g. monitoring of clinical chemistry<br>6. Ease of monitoring<br>7. Length of follow-up<br>8. Risk to health care workers | | | | | | |
| **Design related issues**<br>1. Number of participants required<br>2. Time required<br>3. Bias – internal consistency<br>4. Complexity of intervention<br>5. Interpretability of results<br>6. Suitability for adaptive design<br>7. Ability to maintain privacy and confidentiality | | | | | | |
| **Participant related issues**<br>1. Equitable access (including to vulnerable populations)<br>2. Distribution of benefits and risks<br>3. Acceptability to participants and communities<br>4. Complexity of community engagement | | | | | | |