

## **Note for the record: Consultation on Clinical Trial Design for Ebola Virus Disease (EVD)**

A group of independent scientific experts was convened by the WHO for the purpose of evaluating a proposed clinical trial design for investigational therapeutics for Ebola virus disease (EVD) during the current outbreak, 26 May 2018

### Experts

Sir Michael Jacobs (Chair), Dr Rick Bright, Dr Marco Cavaleri, Dr Edward Cox, Dr Natalie Dean, Dr William Fischer, Dr Thomas Fleming, Dr Elizabeth Higgs, Dr Peter Horby, Dr Philip Krause, Dr Trudie Lang, Dr Denis Malvy, Sir Richard Peto, Dr Peter Smith, Dr Marianne Van der Sande, Dr Robert Walker, Dr David Wohl, Dr Alan Young.

There are many pathogens for which there is no proven specific treatment. For some pathogens, there are treatments that have shown promising safety and activity in the laboratory and in relevant animal models but have not yet been evaluated fully for safety and efficacy in humans. In the context of an outbreak characterized by high mortality rates, the Monitored Emergency Use of Unregistered Interventions (MEURI)<sup>1</sup> framework is a means to provide access to promising but unproven investigational therapies, but is not a means to evaluate reliably whether these compounds are actually beneficial to patients or not. In light of the current Ebola Zaire DRC outbreak with a high case fatality rate, the WHO convened an independent expert panel to evaluate investigational therapeutics for MEURI use<sup>2</sup>, and that panel affirmed the importance of moving to appropriate clinical trials as soon as possible.

Against this background, a clinical trial design has been proposed with a view to generating reliable evidence about safety and efficacy. The proposed design is a **three-arm, open-label, randomized trial** to evaluate simultaneously two candidate therapeutics for laboratory-confirmed Ebola virus disease (EVD). The two primary aims are (1) to compare A versus not-A against a common background of whatever therapeutics are being given, including therapeutic B. This is assessed by comparing A+B versus B alone. (2) to compare B versus not-B against a common background of whatever therapeutics are being given, including therapeutic A. This is assessed by comparing A+B versus A alone. Randomization will be in a 1:1:1 ratio to treatment A, treatment B, or a combination of A+B. The primary aim is not to directly compare A versus B. As A and B work by different mechanisms, it is likely that if one therapeutic is effective it will be of some additional value even in the presence of the other.

WHO convened a meeting of independent scientific experts to help evaluate this proposed clinical trial design. Committee members were provided with a framework for evaluating the trial design for use

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<sup>1</sup> <http://www.who.int/ethics/publications/infectious-disease-outbreaks/en/> Chapter 9 MEURI

<sup>2</sup> <http://www.who.int/emergencies/ebola/MEURI-Ebola.pdf>

during this outbreak. Panel members were free to express their viewpoints and contrary views were listened to respectfully.

A concise summary of key points from the expert panel's deliberations include the points listed below.

- **Endpoint:** Experts agreed that goal of the clinical trial will be to provide the best possible information on clinical effectiveness and safety of therapeutic in the context of an ongoing outbreak. In this case, the primary outcome of 14-day mortality is reasonable.
- **Randomization:** Experts agreed that a randomized clinical trial design is most likely to generate reliable data to evaluate questions about the safety and efficacy of treatments for patients with EVD. Although the randomized clinical trial design that would provide the most interpretable and relevant insights would involve a randomization between a promising investigational treatment and placebo/standard of supportive care, this means some receive no investigational treatment.
- **Placebo-arm:** Most of the expert group indicated a preference for designs where all patients would receive at least one investigational treatment, based on the current status of Ebola therapeutics, knowledge of EVD and the current outbreak. Thus, not including a placebo/standard of care arm alone is considered acceptable in the context of EVD as of May 2018.
- **Proposed 3-arm trial of A vs B vs A+B:** It was proposed, that if a placebo/standard of care arm is not considered to be appropriate, then this design would be the next most appropriate trial design to evaluate efficacy of A and B, where efficacy would be determined by comparing each individual therapeutic to combination therapy. However, there were some concerns: 1) the design makes an assumption of at least some added effect of the combination of A and B, which is not assured; 2) the lack of safety data for combination therapy; 3) feasibility of implementing a 3-arm trial in Ebola Treatment Centres due to its relative complexity; and 4) the impact on sample size in each arm by dividing the patient population in three instead of two groups.
- **Alternative 2-arm A vs A+B trial design:** An alternative to the original proposal was proposed, comprising a 2-arm trial of A vs A+B to evaluate and compare the efficacy and safety of one of the therapies (i.e. B). Some advocated that using a 2-arm design would significantly enhance the ease, feasibility, and rapidity of implementation of such a trial. Of note, it was pointed out that, with respect to the administration of combination therapy, half of all patients in the 2-arm design would receive combination therapy, compared to only a third in the 3-arm design. Also, the 2-arm design is limited as it would give efficacy data on one drug, B, and provide no information on A, whereas the 3-arm trial design would enable evaluation of drug A and B. To be reliably interpretable, prior evidence is required that reliably establishes efficacy of A. In May 2018, there are no drugs that are of proven efficacy for the treatment of Ebola, so the choice of A would be challenging
- **Alternative 2-arm A vs B trial design:** A 2-arm trial comparing A vs B directly, was also discussed. However, the major concern raised was that in the absence of a clear difference in outcomes

between the two arms it may be difficult to judge whether the treatments are equally good or equally poor.

- **Flexibility:** If randomization is impractical for some patients, data collection will continue and that part of the trial will be treated as observational cohort.
- **Safety:** Any trial conducted during this outbreak should have data evaluated by a Data Monitoring Committee periodically. A trial using the same protocol could be used in later outbreaks, if appropriate, with accumulated data being used to address the trial hypotheses using an appropriate meta-analysis methodology.
- **Potential therapeutics:** Although the intent of this meeting was to evaluate study design rather than specific therapeutic agents, it was agreed that therapeutics described in the Notes for Record of MEURI, are reasonable to consider in the trial designs discussed, based on the conclusions of an earlier consultation<sup>2</sup>.

WHO is actively working with Health Authorities in the Democratic Republic of Congo (DRC) to respond to the current Ebola outbreak to minimize harm and loss of life. Supporting clinical research is part of the health operations pillar. The DRC Ministry of Health has designated Institut National de Recherche Biomédicale (INRB) as the lead research coordinator in DRC, and WHO will place particular importance on the MoH and INRB perspectives as those of the affected country.

These conclusions should not be taken as being applicable to other diseases, as each trial design decision will depend on the data and circumstances of the outbreak in question.

The committee will be reconvened as needed.

### List of experts

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### **Assessment of conflicts of interest**

DOI forms were requested from all participants. The DOIs were all reviewed and the following interests were declared:

1. Dr Peter Horby has received grant from Wellcome Trust for conducting clinical trials of Ebola therapeutics, which ceased in 2016. Wellcome Trust does not have any commercial interest in any particular agent. This was not deemed an exclusionary conflict of interest.
2. Dr Robert Walker declared that any travel costs associated with this consultation process would be covered by BARDA. This was not deemed a conflict of interest.
3. Dr Thomas Fleming was a consultant for MediVector in 2015 regarding the use of favipiravir as a treatment for Ebola. He did not provide insight on any particular therapeutic agent, and this was deemed an insignificant conflict.
4. Dr Peter Smith has worked for Sanofi Pasteur (dengue vaccines), Serum Institute of India (N. meningitides clinical trials), and Vaccitech, Oxford (influenza vaccine trials). None of these roles were related to Ebola, and were deemed insignificant conflicts.
5. Dr David Wohl has served on an advisory board for Gilead related to HIV, and has received grants from Gilead for HIV and HCV related work in the past. There were no conflicts related to Ebola.
6. Dr William Fischer is a Principal Investigator on the Prevail IV study which is evaluating the use of GS-5734 in male Ebola survivors with evidence of Ebola virus RNA in semen but has not received any payment or grant support related to this work. He is funded by the NIH for an Ebola survivor longitudinal study and for a longitudinal study of patients with acute Lassa Fever. None of these were deemed significant conflicts of interest for this discussion.