World Health Organization

WHO R&D Blueprint – Ad-hoc Expert Consultation on clinical trials for Ebola Therapeutics

Deliberations on design options for randomized controlled clinical trials to assess the safety and efficacy of investigational therapeutics for the treatment of patients with Ebola virus disease

11 October 2018 - Geneva, Switzerland

Summary of deliberations and next steps

9 November, 2018

R&DBlueprint

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BACKGROUND

As of October 10th, 188 Ebola Virus Disease (EVD) cases (153 confirmed and 35 probable) have been reported in eastern Democratic Republic of Congo (DRC). Of those 66 EVD patients have been offered and received one of the 4 investigational therapeutics on an emergency basis and under compassionate use protocols.

In the context of the current Ebola Zaire outbreak in eastern DRC with a high case fatality rate, individual patients are being offered investigational therapeutics on an emergency basis outside clinical trials and as part of protocols for compassionate use.[1] WHO's guidance "Managing Ethical Issues in Infectious Disease Outbreaks[2]" states that compassionate use of unlicensed therapeutics is only justified when clinical trials cannot be initiated immediately.

Given the size of Ebola outbreaks it is anticipated that one single epidemic may not generate conclusive evidence and therefore it is important to plan for and implement a protocol that would allow the scientific community to collect and accumulate robust evidence over a number of outbreaks over a period of time and to move away from seeing each outbreak as a discrete episode.

Also important is the need to consider the potential operational challenges with the implementation of various trial designs and, with the administration and monitoring of different investigational therapeutic agents. The anticipation of such potential challenges is critical, so appropriate mitigation measures are implemented in advance, if pertinent.

This expert consultation is convening representatives from EVD-at risk countries, international partner organizations supporting affected countries in establishing Ebola treatment centers (ETCs) and providing clinical care, partners and experts in the field of randomized controlled trials (RCTs) for evaluating investigational therapeutics (in particular clinical experts, trialists, and statisticians).

The objectives of this consultation were:

1. To discuss and outline potential criteria that could inform the evidence-based selection of therapeutic agents for clinical trials.
2. To review and critically appraise the existing evidence regarding different investigational therapeutics agents.
3. To discuss trial design options and reach consensus on the various options towards a robust study design.
4. To jointly outline a framework for an efficient collaborative approach across countries and outbreaks.

[1] Update: Consultation on MEURI for Ebola virus disease – 27 August 2018: http://www.who.int/ebola/drc-2018/treatments-approved-for-compassionate-use-update/en/

[2] http://apps.who.int/iris/bitstream/handle/10665/250580/9789241549837-eng.pdf

SUMMARY OF THE DELIBERATIONS AND CONCLUSIONS

On the need to generate randomised evidence

There was consensus on the need to move rapidly and effectively to evaluate the four leading investigational therapeutics available using the most appropriate and practical study design that allows the gathering of robust evidence.

There was consensus on the need for randomized clinical trials (RCTs) and on the choice of a mortality endpoint as a primary endpoint.

On the options for the design of an RCT

Different study designs were discussed during the meeting and in follow up discussions, including a study design currently proposed by the Institute National de la Recherche Biomédicale (INRB) and the National Institutes of Health (NIH), USA in the DRC.

This study is proposed as a multi-center, multi-outbreak, randomized, open-label, controlled clinical trial of experimental Ebola virus disease therapies, each administered with a backbone of optimized standard of care / supportive care (oSOC). Four arms are to be included as soon as possible after the publication of this report. The four arms will include: ZMapp+oSOC vs Drug A+oSOC vs Drug B+oSOC, vs Drug C+SOC.

A three-arm, open-label, randomized trial to simultaneously evaluate two candidate therapeutics for treatment of laboratory-confirmed Ebola virus disease (EVD) was discussed (A vs B vs A+B). The two primary aims are (1) to compare A versus not-A against a common background of optimized standard of care /supportive care, and (2) to compare B versus not-B against a common background of optimized standard of care /supportive care.

Although this is not a regulatory requirement in the US or the European Union, it was noted that there is no available safety data of combination therapy of the proposed investigational therapeutics in animal models. It was proposed that such data would be generated before introducing a combination therapy into a clinical trial.

It was agreed that the protocol must be flexible and adaptive in order to accommodate new experimental therapeutics and/or combination therapy as new evidence emerges. In particular, participants recognized that combination therapy of 2 investigational therapies may demonstrate additive therapeutic benefits. A three-way comparison that would require a smaller sample size could be envisaged as soon as data regarding interaction becomes available.

On the selection of the control arm for an RCT

There were deliberations regarding the use of Zmapp as the control arm given various interpretations on whether the PREVAIL II trial results are inconclusive. Moreover, because the inherent challenges associated with this uncertainty may hamper the possibility to assess the true effect of Zmapp and fail

to reduce the inappropriate use of ZMapp in real world settings, but also because it could lead to a misinterpretation of the efficacy of the other experimental therapeutics.

The participants recognised the methodological strength of using an optimized Standard of Care/Supportive Care arm as the control group, but also acknowledged that in some settings this may reduce the acceptability of the trial and may hinder its implementation. In particular, the current lack of clear definition and consensus on a critical package of optimised Standard of Care / Supportive Care was highlighted as a potential obstacle to this approach. However, it was noted that balanced attention and opportunity for enrolment to the option of an oSOC control should be a consideration in future protocols.

On the evidenced-based criteria for the inclusion of experimental therapeutics in an RCT

Criteria for an evidence-based evaluation of therapeutics to include in the RCTs were presented and welcomed by the participants. Developers of four experimental therapeutics provided data to assess the candidate therapeutics as per the proposed criteria. There was discussion of the various trade-offs of including three or four arms. Some thought that the conceptual questions of monoclonal antibody vs. small molecule drug could be adequately addressed in a three-arm study. Also noted was the challenges of administering some agents. Some noted inclusion of four candidate therapeutics would allow each of the agents to be studied in this RCT that will likely span multiple Ebola outbreaks over the coming years. After further deliberations, it was concluded that all 4 candidate therapeutics (namely Mab 114, Regeneron, Remdesivir and ZMapp) should be included for evaluation in the RCT.

Developers provided assurances that they could supply the treatment courses needed to implement an RCT. In addition, several developers committed to explore new treatment regimens that would simplify administration.

The link between ease-of-administration of an investigational therapeutic and its assessment under an Intention-To-Treat analysis was highlighted, especially in the context of the ongoing outbreak where a majority of patients are admitted in treatment centres at late-stage of disease.

Main conclusions

Following the above deliberations, it was agreed that an amendment to the INRB and NIH protocol would be made to include an additional experimental therapeutic (i.e. Regeneron) as soon as possible after the publication of this report and additional secondary objectives would be added to the protocol also as soon as possible. The protocol would also add a mention about the limitations of the current design and the need for flexibility and adaptation to account for emerging evidence and products.

Secondary objectives of the RCT will include the assessment of the “treatment strategy” i.e. grouped effect of antibody therapy versus antiviral therapy as well as assessing heterogeneities between antibody results. Secondary endpoints would involve virologic and other clinical endpoints in order to explore an effect between groups.

Any modification to the secondary objectives should not delay the implementation of the trial and should be submitted for approval in parallel to the preparations to initiate the trial. It was also noted that the statistical analysis plan will be adjusted to incorporate these amendments.

The above amendments were agreed as an interim approach, in order not to delay the implementation of an RCT during the current Ebola outbreak in DRC.

However, participants concurred on the need to continue to work towards a collaborative approach under a multi-country and multi-outbreak master trial protocol, given that individual trials in one outbreak are unlikely to accrue sufficient end points for robust estimates of the effect of one or more experimental therapeutics.

It was also underscored that there is a need for a clear and transparent decision-making mechanism and governance structure in order to facilitate trial decisions and mediate disagreements between stakeholders. The importance of further empowering and engaging scientists and decision makers from Ebola affected countries in detailed presentations of the key scientific and methodological information was also highlighted.

NEXT STEPS

The following next steps were outlined.

Introducing amendments to the NIH proposed protocol

The NIH team will proceed with the preparations for the initiation of the proposed trial in DRC during the current outbreak, with the commitment that in parallel they will submit asap amendments to the pertinent IRBs and NRAs as described above (i.e. a four way RCT, adding agreed additional secondary objectives, modifying the Statistical Analysis Plan and lastly, clearly indicating the potential to include further adaptations to the design as noted above).

Governance of the trial

The governance of the study would include on the appropriate study committees (Trial Board, Trial Steering Committee, and the DSMB) representatives or nominees from all partners to include the Ministry of Health of DRC, Institut National de la Recherche Biomédicale (INRB) and the National Institutes of Health (NIH), USA, Médecins sans Frontières (MSF), the Alliance for International Medical Action (ALIMA), The African coalition for Epidemic Research, Response and Training (ALERRT) and the World Health Organization (WHO).

Rationale for the choice of the fourth arm – Regeneron Antibody

There was discussion of the trade-offs for including a fourth arm in the current RCT. Adding a fourth arm would spread enrolment across four arms and would increase the time required to accrue a sufficient number of patients in the trial. The trial could address the conceptual question of monoclonal antibody-based therapy vs. small molecule drug treatment without adding a fourth arm. It was also mentioned that each of the investigational products is different, have different dosing regimens and for the

purposes of product licensure would be based on the available data for each of the products; a point in support of adding a fourth arm. The RCT will likely run over multiple outbreaks, so including each of the four investigational products (Mab 114, Regeneron, Remdesivir and ZMapp) provides a chance for data to be gathered on each using the current trial (as opposed to a future trial that might start at some point after the current trial has been completed). Also mentioned were the relative differences in the resources required to administer each of the products in the field with some products having single dose regimens. As noted above, taking these trade-offs into consideration, overall the group's recommendation was to include the Regeneron product as a fourth arm in the current RCT.

Access to Investigational Drugs

It is well recognized that once a clinical trial is in place, use of investigational drugs at clinical trial sites for patients eligible for the trial should be through the clinical trial. Should exceptional circumstances arise where use of an investigational drug outside of a clinical trial is being considered, it's use should not interfere with the ongoing clinical trial. All partners agreed and appreciate the importance to do everything possible to limit the use of therapeutic agents outside the RCT in those sites participating in the trial.

Statistical Analysis Plan

There was discussion of the differing viewpoints on the primary endpoint analysis for the proposed clinical trial to evaluate investigational therapies for the treatment of patients with Ebola virus disease. The ideas for key analyses of the trial included, an analysis that evaluates antibody-based therapy vs. antiviral drug treatment, an analysis that evaluates heterogeneity among the investigational therapies, and an analysis that evaluates each of the investigational agents individually against a selected comparator agent. There were a number of valid reasons discussed for the differing approaches for the primary analysis depending, in part, on the multiple different learnings that can be gained from a trial and how stakeholders with slightly different perspectives might prioritize each of these generally reasonable approaches to analysis of clinical trial data. The point was made that procedural randomizing 1:1:1:1 allowed for each of the different proposed analyses to be possible. It was noted that the use of separate, pre-specified statistical analysis plans is an acceptable means to bridge these differing views of what the primary analysis would be for the clinical trial. Separate pre-specified statistical analysis plans could be on file for the primary analysis of the clinical trial data in order to answer the primary question that was most essential to assess for the stakeholders.

Implementation

This epidemic is happening in an extraordinarily difficult environment and context. Very careful consideration will have to be given to how the trial teams will be deployed in the epidemic zone, under whose authority they will be covered and how their work will be accommodated alongside the epidemic response teams. This will require very close collaboration between DRC, WHO, GOARN, MSF, ALIMA, ALERRT, NIH and all partners.

Revisiting the composition of the trial protocol team

WHO Secretariat will work with NIH to revisit the composition of the protocol team that has been working on the RCT design proposed in DRC in order to ensure that it includes all key stakeholders and experts.

The WHO Secretariat will communicate to its members the agreements reached during the consultation.

WHO Secretariat will make public the composition of the protocol team and will engage to mediate to make sure everyone feels their contributions have been listened to, recognized, documented and agreed upon.

A public sharing of the evidence available and used to inform the inclusion of candidate therapeutics in the proposed RCT

Using the information provided by the developers, WHO Secretariat will prepare summaries of data according to agreed criteria for each experimental therapeutic.

This will help document the evidence-based approach used and add transparency to the process.

A mechanism to facilitate decisions regarding RCT designs

In closing the meeting, it was remarked that there is a need to continue to work towards a collaborative approach under a multi-country and multi-outbreak master trial protocol. Failing to do so will result in individual trials being unable to accrue sufficient data for robust estimates of effect.

It was also underscored that, in addition to the experts` deliberations, there is a need to formalise a clear and transparent decision-making mechanism and governance structure. This would facilitate trial design decisions and mediate disagreements between stakeholders. Such a mechanism should be under the auspices of WHO R&D Blueprint. WHO was asked to propose such a forum to provide a steering mechanism for this required multi-year, multi-country effort.

APPENDICES

Appendix 1. Meeting Agenda

Ad-hoc Expert Consultation on Ebola Therapeutics
Deliberations on design options for randomized controlled clinical trials to assess the safety and efficacy of investigational therapeutics for the treatment of patients with Ebola virus disease
Thursday 11th October 10:30 – 18:30
Co-Chairs: Jeremy Farrar and Edward Cox

Open session

Time	Topic	Proposed speaker
10:00 – 10:30	Welcoming coffee	
10:30 – 10:45	Opening remarks Introductions, Objectives of the consultation	Peter Salama and Co-chairs
10:45 – 11:45	Overview of study design options being proposed to date (15 minutes each) Questions for clarification (15 minutes)	Thomas Fleming Richard Peto Elizabeth Higgs
11:45 – 12:45	Reaching consensus on the choice of a robust study design • Scientific perspectives including choice of comparator arm • Ethical considerations • Statistical considerations • Implementation deliberations • Other	Plenary
12:45 – 13:30	Lunch break	
13:30 – 13:55	Draft criteria for evaluation of evidence and for selection investigational therapeutic agents to include in clinical trials (10 minutes). Questions for clarification (15 minutes)	WHO Secretariat
13:55 – 14:45	Overview of evidence available on the various investigational therapeutic agents (15 minutes) Questions for clarification (35 minutes)	Marco Cavaleri (Developers on line to answer questions)
14:45 – 15:30	Outlining a framework for an efficient collaborative approach across countries and outbreaks. • Generic protocol • Accumulating evidence, data analysis & sharing during and after outbreaks • Overall analysis plan • Other	Plenary
15:30	Coffee break and end of open session	

Closed session

Time	Topic	Proposed speaker
16:00 – 16:30	Conclusions and recommendations on criteria for evaluation of evidence and on selection of investigational therapeutics agents to include in clinical trials.	Plenary
16:30 – 17:00	Conclusions and recommendations on the choice of a robust study design: • Scientific perspectives including choice of comparator arm • Ethical considerations • Statistical considerations • Implementation deliberations • Other	Plenary
17:00 – 17:30	Conclusions and recommendations on a framework for an efficient collaborative approach across countries and outbreaks.	Plenary
17:30 – 18:00	Next steps	Plenary
18:00	Adjourn	
18:15	Cocktail	

Appendix 2. List of Participants

Experts from countries at risk of Ebola

Steve Ahuka Mundeke*
Chef du Département de Virologie
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Sylvanus Okogbenin*
Chief Medical Director
Irrua Specialist Teaching Hospital
Irrua, Nigeria

Experts from Regulatory agencies

Marco Cavaleri,
Head of Anti-infectives and Vaccines
European Medicines Agency
London, United Kingdom

Edward Cox,
Director Office of Antimicrobial Products Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Silver Spring, Maryland, United States of America

Eric Karikari Boateng*
Head, Laboratory Services Department
Ghana Food and Drugs Authority
Accra, Ghana

Other invited experts

Ira Longini
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Department of Biostatistics
University of Florida
Gainesville, United States of America *(will join via TC)*

Michael Jacobs
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Richard Peto
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Oxford, United Kingdom

Thomas Fleming
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Representatives of key WHO Advisory Committees

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Mike Ryan
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Janet Diaz
Health Emergencies Programme

Pierre Formenty
Health Emergencies Programme

Ana Maria Henao Restrepo
Co-lead R&D Blueprint

Vasee Moorthy
Co-lead R&D Blueprint

Marie-Pierre Preziosi
Co-lead R&D Blueprint

** unable to attend*

Appendix 3. Framework and criteria proposed for selection of experimental therapeutics to include in clinical trials

Criteria	*Therapeutic agent*		
	Compliant	**Score**	**Comments**
Mandatory criteria			
1. Preclinical efficacy data in NHP			
2. Safety profile from non-clinical studies			
3. Quality of manufacturing (cGMP)			
Score			
Prioritization criteria			
1. Safety in humans single/repeat dose escalation			
2. Time-efficacy window after challenge in animal models			
3. Dosing rationale			
4. Route of administration and administration challenges			
5. Efficacy data in humans			
6. Access in event of success			
Score			
Additional prioritization criteria			
1. Staff training			
2. Administration and monitoring equipment			
3. Storage & shelf-life			
Score			
Score total			

Appendix 4. Summaries of evidence from selected experimental therapeutics

[to be added]