1st WHO R&D Blueprint Consultation on Therapeutic evaluation in Public Health Emergencies

Executive Summary

On 11-12 December 2017, WHO convened about 30 experts in public health, clinical trials, epidemiology and regulatory to attend the 1st WHO R&D Blueprint consultation on therapeutic evaluation in Public Health Emergencies (PHEs). The meeting was hosted by the University Medical Center Utrecht (UMCU) in Zeist, The Netherlands.

This first consultation aimed to engage participants in a series of efforts to improve the design, implementation, and conduct of therapeutic and prophylactic studies (both clinical trials and observational studies) during Public Health Emergencies, through an inclusive and evidence-based process.

The Blueprint priority pathogens and the current landscape of experimental molecules were used to frame the conversation and illustrate the group's thinking and rationale based on lessons learned from past and current outbreaks.

Participants agreed to initiate a work plan with 4 working groups:
(i) a comprehensive methodological document on therapeutic study designs;
(ii) a decision tree to guide the design of a therapeutic trial and promote discussion around key methodological choices;
(iii) statistical and mathematical methodology for therapeutic and prophylactic studies;
(iv) generic annotated protocols for various study designs.

With respect to the above working groups, participants agreed to develop tools and material during year 2018. A next F2F consultation is planned in Q2 2018 and will provide the opportunity to collectively review activities of the groups.

Introduction

On 11-12 December 2017, WHO convened about 30 experts in public health, clinical trials, epidemiology and regulatory authorities to attend the 1st WHO R&D Blueprint consultation on therapeutic evaluation in Public Health Emergencies (PHEs). The meeting was hosted by the University Medical Center Utrecht (UMCU) in Zeist, The Netherlands. Through this consultation, WHO aimed to promote a scientific discussion on the design, conduct and analysis of clinical trials in outbreaks and to agree *a priori* on standard procedures to rapidly evaluate candidate therapeutics during emergencies, while maintaining the highest scientific and ethical standards.

This consultation was organized as part of the WHO R&D Blueprint plan of action for research preparedness, and builds on tools and material generated under two initiatives dedicated to the evaluation of medical countermeasures: the Blueprint workplan for vaccine evaluation and the GetReal project.

The R&D Blueprint is a strategic plan, which aims to reduce the time lag between the declaration of a Public Health Emergency and the availability of effective medical countermeasures that can be used to save lives and avert crisis. Under the R&D Blueprint, the World Health Organization (WHO) and partners are collaborating to articulate a novel R&D model for emerging pathogens likely to cause severe outbreaks in the near future, and for which few or no medical countermeasures exist. For more information see http://www.who.int/blueprint/en/.

The Julius Global Health program within University Medical Center Utrecht (UMCU) fosters an agenda that leads to strategies, programmes, research and educational activities directed towards improving health, reducing disparities and achieving equity in health. In addition, the UMCU has been the scientific lead for the IMI GetReal project, a public-private consortium consisting of pharmaceutical companies, academia, regulators, HTA bodies and patient organisations. IMI GetReal has developed best practices, robust methods and tools to strengthen real-world evidence collection and synthesis, in order to improve the evaluation of new medicines. For more information see http://www.imi-getreal.eu/.

This first WHO Blueprint consultation aimed:

1. to review methodological work in research preparedness (in particular for study design and implementation) to evaluate therapeutics

2. to review lessons learned from evidence generation and evaluation for therapeutics during past outbreaks

3. to jointly generate a work plan for developing materials and tools for testing a therapeutic intervention (blood products excluded) in the field during outbreaks.

Recognizing both the highest scientific and ethical standards and the fact that the epidemiological reality of PHEs may strongly affect the design of therapeutic studies, the group were invited to answer the following research and public health question: "what can you do when you cannot design the perfect study during a PHE?"

The Blueprint priority pathogens and the current landscape of experimental molecules were used to frame the conversation and illustrate the group's thinking and rationale based on lessons learned from past and current outbreaks.

The Blueprint priority pathogens for 2017 include Ebola/Marburg, MERS/SARS, Lassa, Nipah, Rift Valley Fever, Crimean-Congo Haemorrhagic Fever, Zika and Agent X. The list is revised on a yearly basis through a transparent and standardized process. Those pathogens are typically viral emerging pathogens that cause acute and sometimes lethal infections, with epidemic potential, and for which there is no licensed vaccine, therapeutic or diagnostic. Agent X is listed too to remind us that the next outbreak remains unpredictable and that research preparedness requires both a generic and a pathogen-specific approach.

Lessons learned and Challenges for therapeutic evaluation in PHEs

The group recognized that PHEs provide an extremely challenging working environment that is characterized by many uncertainties, including the lack of knowledge on the pathogen targeted and on the molecules being evaluated, variability in the standard of care in different treatment centres and in other public health interventions. Other uncertainties include the lack of standardization in the field procedures and throughout the clinical development pathway.

The conduct of research as an integral part of the outbreak response is new and requires essential elements of research capacity and international research collaboration, including trust and mutual respect. Among the priority pathogens, the 2013-2016 West-African Ebola outbreak provides an unprecedented PHE where therapeutic evaluation was implemented in the field. It was noted that none of the studies reached their anticipated sample size for assessing effectiveness. Reflecting on that outbreak, participants highlighted operational conditions in the field and governance challenges. They underscored the need for simple, rapid and flexible study designs to address the conduct of research in a resource-limited setting, as well as generating evidence as quickly as possible in in difficult, and sometimes unstable, working conditions.
Participants recognized that outbreaks in which therapeutics may be evaluated may be small-scale. To address realistic sample size in the future, participants discussed different options, including single-arm studies, adaptive trial designs and continuing studies across several outbreaks. Also discussed were model-based approaches, like PK/PD models for dynamic outcomes such as viral load. The framework for designing studies for rare diseases may also be pertinent too. It was recognized that randomization is essential in ensuring comparability among treatment and control groups except for the intervention being evaluated. The need for randomization was discussed in the light of a pathogen case fatality rate and outbreak size, the risk of bias, uncertainties in the research assumptions, and the effect of the expected treatment. Finally, although this is not the main focus of the group, safety assessment cannot be overlooked in study designs, especially as Phase 1 and 2 data may be limited.

In addition to the non-ideal field conditions for therapeutic evaluation, experimental molecules for the treatment of patients with emerging pathogens also exhibit imperfect features depending on the adequate target product profile and a given use profile. Potential therapeutics for viral infections can be split into antivirals and host-response modifiers and can be further categorized depending on which stage they target and inhibit

in the viral replication pathway. Some molecules have demonstrated a broad activity *in vitro* against multiple families of viruses as well as *in vivo* in animal models. However, it is unclear how safety, pharmacokinetic and effectiveness derived from animal models can be extrapolated to humans. Furthermore, laboratory assays, animal models and challenge materials require more validation and standardization in order to better inform on the effectiveness in humans.

Lastly, it was highlighted that drug effectiveness depends highly on the treatment initiation and dosage schedule, especially for acute infections. The prophylactic use of certain molecules could be envisaged in individuals at high-risk of infection or for post-exposure prophylaxis, provided the drugs are reasonably safe and easy to administer. The design of studies to evaluate such interventions would have close parallel to vaccine evaluation for short-term protection. However, there are no preclinical data so far that might support prophylactic use.

Overall, participants recognized that a trade-off needs to be sought between generating evidence in PHEs with respect to the regulatory and ethical standards, and outbreak response objectives, which typically are to eliminate transmission and to provide optimal care to sick people. Finally, research acceptability in the affected communities is key and adequate community engagement strategies and considerations to increase treatment acceptability must be included in study preparations.

Building on existing tools for clinical evaluation

Tools and materials developed under the WHO Blueprint workplan for vaccine evaluation in PHEs were presented to the group, including guidance of major study designs to be used in PHEs, an interactive user-friendly decision tree, infectious disease models to guide vaccine study designs and assess their performance in terms of power and bias, and annotated generic protocols. A framework on how to accumulate evidence across outbreaks for vaccines was also presented and was deemed to be attractive and promising for treatments as well, especially for pathogens for which there might be sporadic or regular small-scale outbreaks . All of the presented tools will go on online for public consultation on the WHO website in Q1 2018, and their principles will be communicated and outlined in peer-reviewed journals. Participants recognized that similar tools can be developed or adapted to provide guidance on treatment evaluation.

A decision-support tool for pragmatic trial design - PragMagic – was presented in an effort to aid in the design of therapeutic trials under specific circumstances in order to increase the generalizability of results while ensuring validity. It was noted that the trial design

elements and focus of that tool can be tailored to the specific context of drug evaluation in PHEs.

Next Steps - A work plan for therapeutic evaluation in PHEs

On Day 2, Participants agreed on a work plan and were partitioned into four groups to initiate the following activities:

(i) a comprehensive methodological document on therapeutic study designs;
(ii) a decision tree to guide methodology experts during the design of a therapeutic trial and promote discussion around key methodological choices;
(iii) statistical and mathematical methodology for therapeutic and prophylactic studies;
(iv) generic annotated protocols for various study designs.

These activities, listed above, will become four working groups. Working group participants have agreed to develop tools and material during year 2018.

A next F2F consultation is planned in Q2 2018 and will provide the opportunity to collectively review activities of the groups. A pathogen-specific consultation will also be organized throughout 2018 to apply the generic tools and material for treatment evaluation to an epidemiologically real situation.