13 November 2014 - Place: Geneva, Switzerland - Following the emergence of Ebola virus disease (EVD) as a severe public health emergency for which no effective therapeutic or prophylactic interventions are available, the scientific community has proposed numerous experimental interventions, including: vaccines; convalescent blood and plasma; and medicines. None of these interventions have been evaluated for efficacy against EVD and therefore clinical studies to assess their safety and efficacy are required.

To facilitate and accelerate the appropriate clinical testing and generation of quality data of potential therapeutic interventions for EVD, WHO convened a meeting of the Scientific and Technical Advisory Committee for Ebola Experimental Interventions (STAC-EE) in Geneva, on 11-12 November 2014. The meeting was attended by experts in Ebola virus, preclinical and clinical testing, pharmacologists, sociologists, public health experts and regulators, as well as representatives from countries in West Africa.

STAC-EE reviewed the data on disease progression and the effect of some experimental products on 18 patients who were evacuated from West Africa to well-resourced facilities in other countries. Resulting data did not permit evaluation of efficacy of these interventions, and the comparatively high survival rate observed in these patients may be due to a variety of factors including the high standard of care they received.

Noting that the standard of care in Ebola affected countries varies between different treatment centres and even in the same centres over time while standard of care is being established, it was agreed that clinical trials should only be conducted in facilities able to provide consistently good standard of care. The number of such sites in West Africa, capable of providing such care and with suitable infrastructure to conduct clinical trials, is limited. Indeed, there have been far more proposals of products to be tested than availability of sites in which they could be tested. It was therefore imperative that STAC-EE prioritize the products for testing, mindful of time pressure and to avoid wastage of resources.

Collecting clinical data under the biosafety conditions required when treating Ebola necessitates careful consideration of the minimum data that should be collected, and since trials may be across multiple sites ideally such data collection forms should be harmonised. One minimal clinical data collection form was presented which will be used by several of the groups planning clinical trials. Other groups indicated a preference to develop a shorter and

simpler form, but which would use several of the same data fields. These forms should be able to permit data pooling at a future date.

In addition, the STAC-EE highlighted the need for rapid Point-of-Care diagnostics to reduce the time gap between sample taking and results being received from laboratories.

Blood products

The Committee was informed of clinical trials of convalescent whole blood (CWB) and convalescent plasma (CP) that are ready to start in two affected countries, and are in planning stages in one, as well as of efforts by the international community to accelerate access to these therapies through capacity building for the national blood transfusion services.

The study in Guinea, organized by a consortium from Belgium, France, Guinea, and the United Kingdom, will evaluate CWB first and switch to CP once supplies become available. An additional study will evaluate CP only. Studies being planned in Sierra Leone will evaluate CP, but also make provision for use of CWB under compassionate use.

The STAC-EE noted that blood from survivors is likely to have variable qualitative and quantitative properties and that assay of anti-Ebola antibody titres for each donation is essential for interpretation of the trial, even if done retrospectively. Standardization of Ebola antibody assays is crucial to enable between-laboratory comparisons of data and reference materials are needed. Standard reporting of outcomes from the clinical trials is also essential and investigators confirmed that data would be collected using standard case report forms. This would facilitate subsequent meta-analysis.

The STAC-EE encouraged further investigation of the option of producing immunoglobulin (IG) from survivors, as IG may have benefits over CWB or CP as a public health intervention. As blood fractionation facilities do not exist in the affected countries, it will be necessary to consider use of facilities in other countries to pursue this option. Finally, it was agreed that reconstruction and then strengthening of blood systems in the affected countries is an important mid-term goal, with multiple benefits, and will provide a long-lasting legacy of the Ebola epidemic.

Medicines

WHO and partners receive daily proposals for potential products against EVD from the scientific community. Many of these have already been tested and shown to have no activity against the virus. It was agreed that these products, excluded for clinical trials at this stage, will be published on the WHO web site to enable scientists and developers to assess themselves whether further investigation is warranted.

One such product, the antiretroviral lamivudine, has been used in some of the affected countries stemming from a belief that it might have therapeutic effects in patients with EVD. However, data presented to the STAC-EE demonstrated that lamivudine has no antiviral activity against EVD and should therefore not be administered for the treatment of Ebola.

Since many products at various stages of development and with varying degrees of supportive data are being proposed to the affected countries and to WHO for consideration for use in the clinic, the STAC-EE developed a set of criteria regarding minimal preclinical and clinical data that should be met in order for a product to be considered for inclusion in clinical trials. This will be published on the WHO website.

While there are several products for which there is strong preclinical evidence (in monkeys) of efficacy against Ebola virus, most of these products are in early stages of development and the process for manufacturing scale-up has not yet been developed, hence, their availability is limited and intermittent. This group includes products such as monoclonal antibodies and small inhibitory RNA. There are other products which present less of a supply challenge because they are easier to make, or are already approved for other purposes, but currently for these the preclinical supportive data generally has shown limited activity either in, in vitro and/or in animal models. This group includes favipiravir, brincidofivir, toremifine and interferons. The committee recognised that the supporting data was weaker, some thought that the comparative ready availability of these products should be taken into account in prioritising such drugs for clinical evaluation, others thought that weak supporting data should lead one to study other drugs and that availability was not a reason to study drugs with weak supporting data.

The STAC-EE reviewed clinical protocols that were presented for trials of these four drugs by different groups, and provided scientific assessment. In addition a common clinical trial protocol for a randomized concurrently controlled study was reviewed. It was noted that there are essentially two proposed trial designs – (1) a historically controlled trial (non-randomized), that depending on the results could, under certain circumstances, lead to a subsequent randomized trial, and (2) the other being a randomized concurrently controlled trial that would start with a best available supportive care control arm, be evaluated using Bayesian analytic techniques, and would be adapted to incorporate an effective anti-Ebola treatment as soon as shown

effective into the standard of care arm that all patients would receive. The feasibility of conduct and data quality derived from the two methodologies were vigorously debated, and it was generally conceded that each method had pros and cons for given situations, but that it was likely that for anti-Ebola treatments that did not have large effects, randomized concurrently controlled trials may be needed.

Of the drugs proposed, it was agreed that there were safety concerns for toremifene which need to be taken into account. It was also suggested that emerging data on brincidofivir should be reviewed by the committee as this may affect the prioritization of this drug, however the data is not yet available.

Next steps

The Committee noted that new data on these and other products are continuously emerging, making it necessary to review updated data in the near future.