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Leslie Kux
Associate Commissioner for Policy
Division of Dockets Management (HFA-305)
US Food and Drug Administration
5630 Fishers Lane, rm. 1061
Rockville, MD 20852

[Docket No. FDA-2015-N-4170; Clinical Trial Designs in Emerging Infectious Diseases]

Dear Ms. Kux:

The Infectious Diseases Society of America (IDSA) appreciates the opportunity to comment on clinical trial designs for emerging infectious diseases. IDSA represents over 10,000 physicians and scientists who are devoted to patient care, prevention, public health, education, and research in the area of infectious diseases and infection prevention. Our members have been closely engaged in the Ebola Virus Disease (EVD) crisis and many lent their time and expertise to help prevent new cases and treat those who were already sick—through public health and medical emergency preparedness activities and direct patient care both here in the US as well as in Africa. Our members also played an integral role in the public health responses to other outbreaks, including the recent emergence of Middle East respiratory syndrome coronavirus (MERS-CoV), the 2012 fungal meningitis outbreak, the 2009 H1N1 influenza pandemic, and the 2003 SARS epidemic.

Infectious diseases specialists are particularly attuned to the rapid importation of infectious diseases facilitated by an increasingly globalized world. Along with our public health colleagues, infectious diseases specialists can bring valuable expertise to public health preparedness and response as well as the clinical and scientific standards that should guide practice.

Well-controlled trials—ideally those randomized and blinded and, in many circumstances, placebo controlled—are essential to assess the efficacy of new therapies or vaccines, even in a public health emergency. There are important lessons from the past on the negative impact of early trials for novel interventions conducted without a placebo arm, including HIV treatments and chemotherapy for breast cancer patients. There are other circumstances, such as trials during influenza outbreaks with pandemic potential, when experience with closely related interventions and correlates of protection allows data from non-placebo-controlled trials to inform decision making on dose, regimen, the need for adjuvant, and other key parameters of potential mass immunization campaigns. However, the power of a study design to provide the robust data needed for decision making must be assessed rapidly and critically based on the specific circumstances of each outbreak and the intervention that the study is intended to guide

2: IDSA comments on clinical trial design to emerging infectious diseases

We acknowledge that it is particularly challenging to assess efficacy of a clinical or public health intervention during an infectious disease outbreak. Outbreaks often are waning before a clinical trial can be initiated and insufficient numbers of new cases may preclude the ability to evaluate the endpoint of efficacy. Without methods to ensure comparability of intervention and placebo groups, outcomes may be biased by differences in risk factors for and/or prior exposure to the infection, underlying health status, unique considerations for pediatric care, and other factors that influence the clinical course of illness. Perhaps most importantly, informed consent is difficult to obtain, particularly when the emergency is associated with high case fatality ratios, such as in the case of EVD.

We offer the following additional comments for your consideration:

Informed Consent

A potential clinical trial participant's false impression of efficacy or inability to appreciate benefits versus risks of a given intervention is a real concern that must be addressed before proceeding with a placebo-based trial during an infectious disease emergency. It is critical any process includes ongoing ethical oversight and active participation from affected communities during both a trial's design and execution.

Mechanisms previously devised for addressing informed consent during emergency scenarios do not translate neatly into solutions for an emergency like EVD. For example, although there are waivers to the requirement for informed consent in emergency settings for certain populations, the scenario of an untested potential therapeutic vaccine given unblinded and without placebos may not fall into this category. Similarly, while community-wide consent prior to an event has been approved for certain emergency conditions that may present to an emergency department in the US, it is likely impossible for public health authorities to establish prior community-wide informed consent for an unforeseeable emerging infectious disease. Regardless of the method of consent, it should be done in a culturally appropriate manner and materials should be developed in collaboration with representatives from the affected populations.

Acknowledging these difficulties, we recommend the creation of specific WHO-approved informed consent protocols. Such an approach could utilize verbal/video information in local languages, aligning closely with informed consent procedures, documenting that a person is so informed and acknowledges his/her desire to participate. In the US, the Common Rule and other US laws and policies related to informed consent for federally-funded research should be amended as necessary to conform to the WHO-approved approach to ensure compatibility.

Additionally, a central or federal "emergency" institutional review board (IRB) process may be considered to provide rapid review and approval during time-sensitive outbreaks. This body could focus on overseeing the design and implementation of such studies in real time during an event as well as ensure closure and ethical oversight of trials wide with widespread distribution and/or allocation of the intervention. IDSA gladly offers its expertise -to develop this process further.

Standard of Care

With no currently available therapy, a sponsor of a placebo-based trial must first ensure that study subjects get the best standard care possible (that which meets or exceeds the locally available standard of care), regardless of whether or not they are assigned to the placebo or treatment group. The incentive for persons to agree to participate in a placebo-controlled trial is the assurance that participants will receive best practice standard of care if they become ill, regardless of group assignment. Indeed, access to the best possible standard of care might have a substantial impact on outcomes independent from the experimental product under investigation. For example, in the case of EBV there is currently a debate occurring among clinical and public health experts as to the best standard of care (e.g., oral vs. IV potassium replacement, administration of broad spectrum antibiotics, use of anti-diarrheal products, etc.). These uncertainties must be addressed and communicated clearly to patients, the community, and the broader public before initiating a clinical trial.

Alternative Placebo-Based Clinical Designs

In certain situations, modified trial designs that can potentially benefit the most people and still provide meaningful data should be considered. For critically ill patients and special populations like children, a treatment decision may need to be made on a case-by-case basis, carefully balancing the risk of the treatment, the biological plausibility of a beneficial effect, and the pre-clinical or observational data. Alternative placebo-based trial designs may facilitate this balancing process. For example, adaptive trials have been proposed which would allow investigators to plan a staged study or series of studies and make modifications as more is learned about the effectiveness and safety of the therapy. Alternatively, 3-to-1 matching of active to control arm designs may take longer to get an answer, but more people at risk of the lethal disease would get the potentially beneficial product. Ultimately, the impact of an intervention over the course of an outbreak can best be evaluated after the intervention has been proven to be effective at an individual level.

IDSA appreciates the opportunity to comment, strongly agrees that a comprehensive discussion is needed to ensure that interventions are rapidly, safely, and ethically evaluated for effectiveness in the event of an emerging disease outbreak. We offer our expertise to further aid the Agency in these efforts. If you have any questions, please contact Greg Frank, IDSA Program Officer for Science and Research Policy, at 703-299-1216 / gfrank@idsociety.org.

Sincerely,

A handwritten signature in black ink that reads "Johan S. Bakken MD, PhD". The signature is written in a cursive, slightly slanted style.

Johan S. Bakken, MD, PhD, FIDSA
IDSA President