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Conducting Clinical Trials in Outbreak Settings: Points to Consider

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Background

In the summer of 1981, the U.S. Centers for Disease Control and Prevention reported cases of a rare respiratory infection, *Pneumocystis* pneumonia and an unusual cancer, Kaposi's sarcoma, in young, previously healthy homosexual men in Los Angeles, New York, and San Francisco. The underlying reason for these infections, immune compromise due to infection of immune competent cells by the human immunodeficiency virus (HIV), would not be understood for three more years with the discovery of HIV, and the global impact of the virus would take many more years to elucidate. Still, even in the earliest days of the HIV/AIDS pandemic, the near-inevitable mortality associated with the disease was clear. Affected individuals and their caregivers were desperate to find effective treatments, and many tried unproven interventions that would sometimes cause more harm than good. Biomedical researchers experienced intense pressure to offer access to experimental therapies in the face of near certain death.

Most investigators felt that interventions for HIV/AIDS should be tested according to sound scientific principles, using the "gold standard" of double-blinded, randomized, placebo-controlled trials to determine the safety and efficacy of candidate therapies. Prioritization for testing of drugs was based on a careful analysis of available preclinical data. This approach yielded a solid basis for the testing and ultimate proof of efficacy of the first approved antiretroviral drug, zidovudine (AZT), and other agents to treat HIV and its complications in the early years of the HIV/AIDS pandemic. However, some stakeholders felt that strict adherence to scientific practices was unnecessary and insisted upon immediate access to any therapy with a remote chance of making a difference. Eventually, through extensive dialogue and engagement of scientists, regulatory agencies and the affected communities, a compromise was reached whereby first priority was given to rigorous evaluation of the most promising treatments with immediate expanded access to those treatments upon demonstration of efficacy. The HIV/AIDS experience provides a paradigm for conducting clinical trials in other emerging epidemics, such as the Ebola outbreak of 2014-2015 in West Africa.

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Core Principles

When testing medical countermeasures in an outbreak setting, the biomedical research community must hold fast to the core scientific and ethical principles delineated below. This will help, not hinder, efforts to quickly and definitively determine the safety and efficacy of interventions and thus provide access for the greatest number of patients to the most effective therapies in the shortest possible time. While adhering to those principles, researchers must also be mindful of the needs, concerns and opinions of affected communities and introduce flexibility, where possible, into the process.

The context in which research is conducted is always an important consideration. Outbreaks of emerging infectious diseases, particularly those of the scope experienced with Ebola in West Africa, demand a multi-sectoral, international effort, focused first and foremost on a robust public health response. That response must include prompt identification, and, where appropriate, isolation of suspected cases, careful accounting and tracing of contacts, safe care for infected individuals and, in the case of Ebola, hygienic and culturally sensitive burials. Public health efforts must remain at the forefront of the overall outbreak response. However, the conduct of biomedical research can also be an important and discrete component of the response. Research evaluating potential countermeasures, including vaccines and therapeutics, must be conducted in a scientifically and ethically sound manner to reach definitive conclusions about efficacy and safety as expeditiously as possible. To accomplish this goal, it is essential to articulate some core principles that can be used to guide such trials.

The ethical principles formulated for research in general in developing countries serve as a useful guide for analogous principles in outbreak situations in such settings (Table 1).[1] The overarching goal of these principles is to avoid exploitation of trial participants or local research partners. Additional tenets stem from that primary goal, including respect for volunteers and study communities, the value of informed consent and the need for collaborative partnership with affected communities.

Partnerships are particularly important in outbreak situations and the local realities of outbreaks can complicate the development of these relationships. For example, in the case of the Ebola epidemic in West Africa, while the governments of affected countries were interested in partnerships with the United States government and other research sponsors the most effective way to establish those partnerships was less clear. First, in the case of government-to-government partnerships, a diplomatic invitation is an extremely helpful first step. In the case of the Liberian-U.S. partnership, this occurred via an invitation from the Minister of Health of Liberia to the Secretary of Health and Human Services of the United States. Second, the in-country capacity to conduct clinical research must be carefully evaluated, including identification of interested local investigators and assessment of existing trial infrastructure. In Liberia, infrastructure was minimal, and needed building. This was undertaken with a goal of long-term sustainability. Third, regulatory oversight may need to be bolstered. The Liberian-U.S. government partnership extended beyond research institutions to regulatory bodies in both countries. Today, a lasting clinical research partnership has been established between the governments of Liberia and the United States,

the Partnership for Research on Ebola Virus in Liberia (PREVAIL). Our Liberian counterparts are leading an effort to expand PREVAIL into a research network involving other countries in the region. While formation of strong local partnerships and local capacity is a resource- and time-intensive process, it establishes the fundamental infrastructure for conducting ethically and scientifically sound trials in the setting of the current outbreak and in the future.

Although partnerships are necessary, they are insufficient in and of themselves. Clinical trials of medical interventions in outbreak situations also must ensure that the agents to be studied have plausible benefit, and that the trial designs being employed are scientifically sound. Together these concepts form the basis of scientific validity.

In evaluating the issue of plausible benefit, investigators must take into account all preclinical and clinical information regarding a candidate therapeutic or vaccine, including existing safety and efficacy data and practical considerations such as ease of administration in challenging settings. Planning for a medical countermeasure study under the auspices of PREVAIL provides an illustrative example. In November 2014, investigators and regulators met individually with representatives from companies developing anti-Ebola medical countermeasures and reviewed available animal and *in vitro* data. They also examined existing safety profiles, including data drawn from use of drugs for other indications, such as with the use of the antiviral drug brincidofovir for adenovirus infection. On the basis of these discussions and consideration of available drug supplies and supply chains, candidates were prioritized for evaluation in a randomized, controlled treatment study, which employed an adaptive design comparing optimal standard of care to optimal standard of care plus a countermeasure.[2] When the trial was launched in February 2015, investigators had confidence that they were testing the most promising candidate at the time – the cocktail of monoclonal antibodies known as ZMapp.[3]

In evaluating the issue of scientific validity, a reasonable expectation of safety and efficacy is critical, and so too is the design of the clinical trial. It is important that studies be designed in close collaboration with local partners with the goal of reaching a definitive answer regarding the safety and/or efficacy of a candidate vaccine or therapeutic. There must be a clearly articulated primary endpoint that is defined before trial initiation. Moreover, robust statistical practices, including sound power calculations, must be employed (based on the best available knowledge regarding efficacy of the candidate as well as the underlying epidemiology). Intention-to-treat analyses are important to minimize misrepresentation or over-interpretation of results. Operational procedures should be defined *a priori* to reduce bias, and an effort should be made to include data from all participants rather than excluding some individuals *post hoc*. If possible, study personnel should be independent of the clinical care team and the interventions being compared should be blinded, in order to avoid bias.

It also is important to point out the importance of a prospectively enrolled control. Historical controls have been attempted in outbreak settings, but the inevitable changing nature of incidence (when one is evaluating a vaccine) and the variability and changes in the local standard of care (when one is evaluating a therapy) compromise the validity of this method.

Proper study oversight is as important as rigorous study design. In addition to review by an independent Institutional Review Board or equivalent, an independent Data and Safety Monitoring Board (DSMB) should be appointed when dealing with a trial in which the investigators are masked as to treatment assignment. It may also be advisable in certain other circumstances such as high-risk or high-profile studies. The DSMB should include broad representation from subject matter and clinical trial experts, should represent the populations that stand to be affected by the result of the study and should be free of influence from trial personnel and sponsors. Further, it should meet on a regular basis, at appropriate intervals based on the study design and enrollment rate. These meetings should conclude with formal guidance to the investigators regarding trial modification (as necessary to meet the primary endpoint) and advisability of continuing the trial. In the event that the DSMB decides that the trial should be stopped, whether due to successful early attainment of endpoint, futility or even evidence of harm, as much data as possible should be rapidly shared with the public in order to promote transparency and appropriate action by health authorities.

Transparency itself is a core principle that must guide trials in outbreak settings. When a study is concluded earlier than anticipated, in addition to the announcement of study closure, every effort should be made to share the data prompting that decision. Returning to analogies with HIV infection, this approach was taken following DSMB recommendations for early termination in two HIV clinical trials: the early stops to the Strategic Timing of AntiRetroviral Treatment (START) trial[4] and the HIV Vaccine Trials Network (HVTN) 505 trial.[5] In the first case, the results showed benefit, but in the latter, the results showed no benefit and possible harm in terms of increased risk of acquisition of HIV among vaccinees (a concern that was alleviated in subsequent follow up). In these cases, the nature of the news did not influence the decision to share the data, and data sharing preceded publication in the scientific literature in both cases. While timely peer-reviewed publication should follow DSMB action, publication must not be allowed to delay dissemination of findings and potential resultant changes in clinical practice or public health actions. Moreover, data must be shared promptly with regulatory agencies in order to promote an orderly and timely evaluation of the findings, regulatory approval where appropriate, and opportunities for expanded access in the event an intervention shows benefit. Any publications that do result should be offered in an open-access format or be made freely available to promote sharing with practitioners and policymakers.

The principles outlined above can serve as a set of guidelines for the conduct of clinical research in an outbreak setting. It is also important that such efforts be well coordinated within the international community in a setting of clear governance that enables rapid decision-making. Otherwise, prioritization is difficult, counterproductive competition is almost inevitable and, unfortunately, exploitation becomes a real risk. As the international body responsible for coordinating health aspects of outbreak response, the World Health Organization (WHO) seems a logical place to house coordination of clinical research. During the Ebola outbreak, the WHO served as a convener of investigators, product developers and research organizations, with participation from affected countries. While providing a common source for information, by not clearly prioritizing investigational agents, this process enabled a wide array of activities of varying degrees of value. The WHO

has an opportunity to serve a critical role in this setting by facilitating an objective prioritization of research studies and rapid dissemination of subsequent findings.

Research conducted in outbreak settings is essential to identifying improved responses to emerging diseases, particularly medical countermeasure research. However, investigations must be thoughtfully undertaken with the highest ethical and scientific standards in order to increase their likelihood of success and reduce the chance of inadvertent harm to study populations. Definitive studies lead to more rapid licensure and, hopefully more rapid distribution of new vaccines and treatments. To that end, the core principles outlined above can serve as a set of guidelines that can be adapted to meet the unique aspects of an individual situation. With this approach, investigators will respect the contributions of the study volunteers by ensuring that their participation has a chance to improve our responses to current and future outbreaks.

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Table 1

Core Ethical and Scientific Principles for Trial Conduct in Outbreak Settings*

Ethical conduct to avoid exploitation – including respect for volunteers, local community engagement and carefully informed consent
Partnership with affected country investigators and officials – including identification of interested local investigators, bolstering of trial infrastructure as needed and shared best practices regarding regulatory oversight
Scientific validity – including plausibility of benefit from candidate countermeasures and sound trial design
Independent review and scientific oversight – careful oversight by an independent and skilled Data and Safety Monitoring Board
Transparency – prompt sharing of data with practitioners and affected communities

* Adapted in part from Reference 1