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Ebola Clinical Trials: Five Lessons Learned and A Way Forward

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Abstract

Background—Little progress was made in advancing Ebola-specific therapies during the epidemic that began in West Africa in late 2013. Throughout the last quarter of 2014, which saw the greatest numbers of cases, only a handful of clinical trials were underway. Subsequently, as incident cases dwindled, the number of clinical trials increased dramatically, but few, were destined to recruit to their accrual targets. The predictable barriers to implementing clinical trials in resource-constrained settings are compounded by unique characteristics of Ebola — including its high fatality rate, its swift transmission through populations, and the grave risks for exposed health care workers.

Methods—As members from a group hastily configured as the Ebola Clinical Research Consortium, we sought to implement two clinical trials beginning in late 2014 in Liberia and Sierra Leone: one to evaluate the efficacy and safety of convalescent plasma for Ebola treatment ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT02333578) Identifier: NCT02333578) and another, an adaptive platform protocol to evaluate multiple treatments for Ebola Virus Disease ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT02380625) Identifier: NCT02380625).

Results—Here, we offer five lessons learned from our experiences that may help inform future efforts to conduct clinical trials targeting Ebola or Ebola-like outbreaks: (1) Research should be an integral part of the public health emergency response in outbreak settings; (2) conducting emergency clinical trials requires experienced research staff at all levels from the start; (3) public

health officials should coordinate with scientific leadership to direct resources towards the most meritorious research questions; (4) a platform trial design is well-suited to ethically and efficiently identify effective therapies in the setting of a high-fatality, dynamic outbreak; (5) to advance therapeutics in the midst of an emerging outbreak, academic and research communities need to respond as boldly and as swiftly as the humanitarian community.

Conclusions—Clinical research to evaluate Ebola therapeutics in the West Africa Ebola epidemic was initiated too late to yield optimal results. In seeking to conduct two clinical studies in this region, we learned valuable lessons and suggest a way forward for implementing therapeutic clinical trials in the next epidemic.

Keywords

Ebola; clinical trials; platform clinical trials; response-adaptive randomization

You learn how to cut down trees by cutting them down.

—Bateke proverb

Compounding the tragedies of over 11,000 deaths and the untold economic and societal impact of Ebola in West Africa, is the reality that some of the best-designed, most scientifically rigorous clinical research efforts were initiated too late to yield meaningful data. We sought to implement two clinical trials in the midst of the Ebola outbreak in Sierra Leone and Liberia: one to evaluate the efficacy and safety of convalescent plasma for Ebola treatment ([ClinicalTrials.gov](#) Identifier: NCT02333578) and another to evaluate multiple treatments for Ebola Virus Disease ([ClinicalTrials.gov](#) Identifier: NCT02380625). Although neither study is destined to reach accrual targets, reflection on their development and implementation may be instructive for policy makers, clinical trialists, and on-the-ground research staff. Here, we offer 5 lessons learned, each with an eye towards the future.

1. Research should be an integral part of the public health emergency response in outbreak settings

Despite witnessing more than 26,000 cases of Ebola in the 2013–2015 epidemic, the clinical development of therapeutics for patients suffering from Ebola Virus Disease (EVD) advanced very little. While improvements in supportive care, such as the use of intravenous fluids and the empiric treatment of comorbid conditions, may have contributed to declines in EVD mortality in the latter stages of the epidemic, therapies targeting EVD itself were not adequately evaluated. Perhaps a primary reason for the slow response of the research community was the sentiment that the epidemic would ‘burn out’ just as precious resources were being mobilized. However, even after the WHO declared the epidemic to be a “public health emergency of international concern” in August 2014¹ and after stark predictions for the epidemic were made by leading groups such as the the US Centers for Disease Control and Prevention (CDC) in September 2014,² the research and research funding communities were relatively slow to mobilize and to operationalize clinical trials in West Africa. Figure 1 underscores the point graphically. The primary y axis shows World Health Organization (WHO) derived estimates of the weekly number of cases of Ebola in the Liberia, Sierra Leone, and Guinea, and the secondary y axis shows the number (cumulative, by start date)

of clinical trials conducted in West Africa, as registered at [clinicalTrials.gov](https://clinicaltrials.gov). The obstacles to conducting emergency research in resource-poor settings are not trivial and include obtaining timely research clearances, forging new collaborations, training research staff, negotiating material transfer agreements, sourcing and importing drugs and sophisticated equipment, and ensuring access to a reliable power grid and back-up generators for sensitive equipment. In addition, extensive scientific deliberations are required to select candidate therapies and to optimize clinical trial designs to deliver answers as swiftly as possible in a rapidly progressive epidemic.

Moving forward, some (but not all) of these obstacles could be addressed with thoughtful coordination of research and clinical care plans as emergency response strategies are developed. Although the tasks of humanitarian responders and research responders differ, they both, for instance, require adequate infrastructure (power supplies, space, housing, security and communications) as well as the ability to rapidly source and import critical supplies, and they ultimately have the same goal: to improve the outcome of those suffering from disease.

The efficiencies gained by sharing such infrastructure and coordinating supply chains, should free up each group to be more effective. Equally, if not more importantly, the research community needs to actively participate in the development of emergency humanitarian responses to facilitate this collaboration and to discuss key research objectives from the outset, or better yet, during inter-epidemic periods. Because the necessary administrative, ethical, and regulatory procedures required for research vary by country and can be challenging to navigate, it is imperative that at the earliest stages possible, outside researchers engage with appropriate local stakeholders in healthcare, public health, academic and governmental sectors and that this engagement be led by a trusted, well-respected collaborator who is also involved in emergency response efforts.

2. Conducting emergency clinical trials requires experienced research staff at all levels from the start

Many local and international first-responder colleagues are not familiar with clinical trials methods, Good Clinical Practice (including standards for research subject protection), and key principles of regulatory and data management. Moreover, such first responders typically are already occupied with immediate tasks of caring for patients under their charge, and some may be willing to accept personal risks involved in providing direct care for Ebola patients, but less willing to accept additional risks to advance research. Thus, simply co-opting clinical staff for research tasks may not be feasible or advisable, especially in the early stages of the research response. Building biomedical research capacity in resource-limited settings is a critically important task. As a matter of timing, however, in a dynamic outbreak setting in which there is little existing research expertise and the window of opportunity to evaluate and advance new therapeutics is unpredictable, the conduct of scientifically rigorous clinical trials that can efficiently deliver results must be prioritized.

Consequently, research teams with the requisite training, expertise and cultural sensitivity, should be deployed early in the epidemic to liaise with clinical responders, establish clinical

care-research partnerships at strategic sites, and implement protocols. Such teams will vary in composition, depending on the nature of the clinical trial, but should include clinicians with clinical trials expertise, clinical research nurses, laboratory specialists, and logisticians. Personnel with administrative and regulatory expertise will be required both locally and internationally to promptly report serious adverse events, clinical endpoints, and other information to local and international regulatory agencies. In addition, appropriate clinical trial monitoring must be arranged. During and after the implementation of emergency clinical trials, local capacity must be strengthened and reinforced through collaborative relationships between local first responders, public health entities, academic institutions, and the research community. The trust and mutuality established early on between these stakeholders will facilitate ongoing and future research activities.

3. Public health officials should coordinate with scientific leadership to direct resources towards the most meritorious research questions

In the absence of proven effective therapies and few experts, the landscape of candidate investigational products may be unduly influenced by individuals with pecuniary interests and/or an anchored bias towards one particular product or approach. Consequently, unconventional therapeutic approaches for which there is no scientific evidence (e.g. ozone therapy and garlic) may be considered on par with other interventions for which there is strong pre-clinical scientific rationale. Some clinical sites could be perversely incentivized to establish research collaborations based on resources promised, political pressure, or simply the powers of persuasion of prospective researchers — rather than a careful evaluation of the merits of the science or the potential benefit for patients. Some decision-makers at clinical sites may not have the expertise to evaluate the scientific merits of the research being proposed. Precious resources of time, clinical sites, and research subjects must be allocated to therapies and approaches that demonstrate (a) the most promising objective pre-clinical and clinical safety data and (b) have potential for wider distribution if proven effective.

To best steward these resources, evidence-driven ‘go’ or ‘no-go’ decisions for a particular intervention must be made, and difficult decisions to halt a given study or to shunt resources towards a more favorable one may even be necessary. This approach requires that national public health and research leadership be tasked to evaluate emerging international research guidance (including from the WHO) in light of the local context, liaise with international research groups, and regularly review the research landscape and research findings as they become available. These reviews should be done with transparency, scientific rigor, and should be free from political pressures at any level. One suggestion to circumvent such pressure is for researchers to meet regularly and frequently with political leadership to communicate their progress and ongoing commitment to the public good. Ideally, the majority of the therapies being evaluated in an outbreak setting would be under the umbrella of a platform trial (*vide infra*) that includes its own therapeutics evaluation committee.

4. A platform trial design is well suited to ethically and efficiently identify effective therapies in the setting of a high-fatality, dynamic outbreak

Traditional, randomized controlled trials are most practical for answering dichotomous decisions about drug safety and efficacy in reference to pre-specified outcomes, but this approach may not be optimal for evaluating therapeutics targeting a disease that is highly fatal, moves swiftly through populations, and for which no specific therapy has been established.^{3, 4} In the context of an outbreak such as Ebola, particularly when the therapeutics landscape is severely limited, but predicted to change rapidly, alternative clinical trials designs that offer greater flexibility and efficiency, and that maximize the likelihood of benefit to clinical trials participants, merit serious consideration. The platform trial, which is designed to evaluate multiple treatments and can accommodate the addition of new treatment arms during the trial, is well-suited for this circumstance.⁵ In addition, instead of stopping the entire trial for pre-specified measures of success, futility, or harm, using Bayesian methods, ineffective treatment arms can be removed during the course of the trial, and response-adaptive randomization strategies can be used to increase the probability that a given research participant will benefit from an emerging effective therapy.^{6, 7}

Based on experiences in Liberia and Sierra Leone, we believe the practical advantages of the platform trial design are significant, but they will only be realized in settings: (a) where multiple equally-ranked candidate therapies exist; (b) where there is strong, centralized public health and research leadership (see #3 above); (c) where disparate groups advocating for different treatments are willing to ‘put their product on the line’ for evaluation in this design, rather than in competing, separate clinical trials; (d) where there is robust, centralized data and statistical management that can accommodate near-real-time endpoint evaluation (thus facilitating response-adaptive randomization and the ability to prune ineffective treatment arms); and (e) where there is careful monitoring of the adaptive trial data by an independent data monitoring committee and of the therapeutics landscape by an active therapeutics evaluation committee.

5. To advance therapeutics in the midst of an emerging outbreak, academic and research communities need to respond as boldly and as swiftly as the humanitarian community

Organizations such as Médecins Sans Frontières (MSF), Samaritan’s Purse, Partners In Health, International Medical Corp (IMC) and others, mounted unprecedented responses, swiftly allocating financial and personnel resources to address the emerging Ebola epidemic. Clinical care teams were vetted, trained, and placed in the field to care for growing numbers of patients, and organizations and individuals assumed considerable corporate and personal risk in order to respond rapidly. Academic and research communities must be prepared to respond equally boldly and assume similar risks. The conduct of clinical trials, particularly in a new setting and with a new research question, requires careful advance planning that spans a host of domains — rigorous study design, robust data management and statistical support, ensuring high quality laboratory and pharmaceutical support, ethical and Good Clinical Practice training, study monitoring plans, data management, and ensuring

community engagement. For the research community to respond effectively, swiftly — advance preparations will be required.

Moving forward, a rapidly deployable team of qualified personnel from academic and research organization should be identified and funded to implement platform-protocols that are ‘at the ready’ for the next outbreak. Research teams necessarily would include logisticians, administrative coordinators, research nurses, pharmacists, data managers, regulatory specialists, and investigators. Not all would need to be in the field, but all would need pre-approval from their employers to rapidly re-allocate effort to engage in emergency research protocols. All members would be trained on protocols, receive safety training, and be willing to assume the same risks that clinical first-responders assume in caring for patients with Ebola. Those who would deploy to international sites would do so as teams, having established and honed standard operating procedures, roles, and communications through team-based exercises analogous to those conducted by United States National Guard units and Homeland Security domestic preparedness groups.

Conclusion

To put the Bateke proverb in a different context, in conducting clinical research in Sierra Leone and Liberia during the 2013–2015 Ebola, we learned something about conducting clinical research during an outbreak. In order to advance therapeutics in the next Ebola or Ebola-like outbreak, experienced research teams who are mission-ready, having prepared during inter-epidemic periods, and able to deploy on short notice should coordinate efforts early with humanitarian first-responders and in collaboration with strong, local scientific and public health leadership. With advanced preparation and adequate data and statistical support, flexible clinical trials designs, such as the platform clinical trial, should be readily adapted and implemented to evaluate new and emerging therapies in the outbreak setting.

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Figure 1. World Health Organization estimates of Ebola cases in West Africa and Ebola clinical trials located in West Africa as registered at ClinicalTrials.gov.