SOUNDING BOARD

Creating a Framework for Conducting Randomized Clinical Trials during Disease Outbreaks

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Conducting trials of novel interventions during infectious disease emergencies, such as the ongoing Covid-19 pandemic, is increasingly recognized as important for determining the efficacy of potential vaccines and therapies. Clinical trials to evaluate investigational interventions are being implemented as part of the broader efforts to control the spread of an infectious disease and to improve patient outcomes. In such circumstances, however, it can be challenging to acquire the necessary evidence about the effects of the interventions to inform future patient care and public health planning, in part because of the unpredictable size, geographic location, and duration of outbreaks.[1]

TO PUBLISH OR NOT TO PUBLISH

Concern about publication bias has led to an emphasis on the need to report the results of all clinical trials, even those that end early with inconclusive results at the end of an outbreak. This principle is included in statements regarding the ethical framework of clinical trials, such as the Declaration of Helsinki. Following this principle, investigators in trials that were conducted during the 2014–2016 West African Ebola epidemic that were terminated early (without reaching predefined stopping criteria) because of waning transmission submitted the inconclusive results for publication as planned at the end of the trial.[2-4] Avoidance of publication bias is essential for the development of good policy; nonetheless, publication of inconclusive results (e.g., from an underpowered study) can make it much more difficult to develop definitive evidence about the efficacy and safety of the intervention under investigation.[5,6]

At the end of an outbreak, the release of promising but inconclusive results from partially completed trials may support the belief that confirmatory trials comparing the investigational agents with the previously accepted placebo or standard-of-care comparator could no longer be conducted. This assumption can create a state of perpetual uncertainty about the true effect of both the previously tested agent (which may now be considered the standard of care) and any new agents that are being evaluated. This situation has occurred, for example, with the routine off-label use of ribavirin for the treatment of Lassa fever[7] and of oseltamivir for the treatment of severe influenza.

In the randomized, controlled PREVAIL (Partnership for Research on Ebola Virus in Liberia) II trial of the triple monoclonal antibody cocktail ZMapp, the investigators concluded that "although the estimated effect of ZMapp appeared to be beneficial, the result did not meet the prespecified statistical threshold for efficacy." The evidence of efficacy clearly did not meet the conventional standards for licensure.[4] Nevertheless, in 2018, during a large Ebola outbreak in the Democratic Republic of Congo (DRC), investigators used ZMapp rather than the standard-of-care treatment as the control against which to compare other Ebola therapeutics in the randomized PALM trial (Investigational Therapeutics for the Treatment of People with Ebola Virus Disease).[8]

There is an obvious need to balance the importance of publishing the results of all completed

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clinical trials against the potential adverse consequences if the published results do not provide reliable answers to the questions that the trials were designed to address. Thus, a new approach to clinical trials is needed to enable reliable evaluations of vaccines and treatments for outbreak pathogens.

INTRODUCING THE CORE PROTOCOL

As members of the R&D Blueprint,[9] a work plan for designing clinical trials during public health emergencies, sponsored by the World Health Organization (WHO), we advocate the use of a "core protocol" in such cases. Core protocols (also called master protocols) have been described for simultaneous evaluation of multiple interventions or of a single intervention targeting multiple diseases.[10] We propose a core-protocol concept that allows a clinical trial to extend across multiple infectious disease outbreaks. This approach accommodates the changing and unpredictable features of an epidemic and incorporates new investigative team members into the trial over time.

To avoid a premature release of data, core protocols would specify that efficacy data from a trial that has not yet been completed because of insufficient enrollment should not be released. After an outbreak has ended at a given site, the trial would be paused. If so specified in the core protocol, an independent monitoring committee could review results from an interim analysis of trial data to make recommendations regarding whether the trial should continue or stop for efficacy, futility, or safety, as guided by a prespecified monitoring plan.[11] Under the core protocol, the investigators would remain unaware of any results of the analyses; the trial data would be released only if the trial was stopped on the basis of a recommendation from the monitoring committee or had reached its targeted number of endpoint events or amount of participant follow-up.

Vaccine trials that are conducted for 2 years or more are commonly performed to combat diseases with predictable seasonality, such as Lyme disease[12] and Argentine hemorrhagic fever,[13] with results withheld until the requisite numbers of events have been observed. Such studies provide some precedent, albeit imperfect, for our proposal, which differs in that it focuses on diseases with outbreaks that are less predictable, may not be observed every year, and may reemerge in a different location. Such diseases include those targeted by the R&D Blueprint — including Ebola virus infection, Middle East respiratory syndrome, Lassa fever, and Nipah virus infection — that occur irregularly but nonetheless relatively frequently. For pathogens that may emerge only once a decade or even less frequently, this approach may not be practical.

The use of core protocols can facilitate the implementation of clinical research across successive outbreaks. The PALM trial included a core-protocol framework to guard against the release of inconclusive data. If the outbreak in the DRC had waned before the conclusion of the trial, the trial would have continued without a release of the results, unless the data monitoring committee had recommended termination. Ultimately, the PALM trial was terminated during the DRC outbreak on the advice of the data monitoring committee when an interim analysis revealed that REGN-EB3 (another cocktail of three monoclonal antibodies) was superior to ZMapp; improved survival was also associated with the monoclonal antibody mAb114 but not with the nucleotide analogue prodrug remdesivir.

Although the PALM trial was successful in identifying two promising therapeutics, there were limitations resulting from the use of ZMapp as the comparator group because its clinical benefit had not been definitively established during the PREVAIL II trial. The overall evidence in support of REGN-EB3 and especially mAb114 would have been stronger if the drugs had been evaluated against a standard-of-care group, as in the PREVAIL II trial, or a drug with known efficacy. Furthermore, the question remains whether ZMapp and remdesivir have any effect. Such findings would have been particularly valuable in settings in which the monoclonal antibody drugs were not available and would have had implications for the development of combination regimens. Finally, it is not clear how data from the PALM trial would have been interpreted if survival had been similar in patients receiving the other drugs and in those receiving ZMapp. These challenges could have been largely avoided if the PREVAIL II trial had been designed under a core protocol. It is likely that the results of the PREVAIL II trial would not have been published at the end of the epidemic, since they did not meet the prespecified level of evidence required, and the trial would have been restarted in the DRC with a standard-of-care group

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in place plus ZMapp and additional investigational treatments. With accrued data from the DRC, the question of whether ZMapp was effective could have been answered, thus establishing a clearer benchmark for all candidate products. Such a framework could also have eliminated the need for a new protocol altogether.

EMPHASIS ON COOPERATION AND COORDINATION

The development of a core protocol involves a preliminary step of engaging researchers and national representatives from affected countries in determining the primary research questions and main design elements. Since officials in the Ministry of Health and other governmental offices in affected countries will be under great political pressure to release the interim results of trials, their approval of the strategy is necessary. Ethics committees and regulatory agencies should be engaged in the earliest stages of protocol planning. There must be a clear and transparent a priori mechanism for achieving consensus regarding elements of the protocol, such as the selection of investigational and control agents and the governance structures to oversee trial operations, manage data and samples, and mediate disagreements among the stakeholders. An international organization, such as the WHO, may be best suited for the responsibility of coordinating stakeholders and maintaining capacity for research over a time period of uncertain duration.

For each successive outbreak, study teams should be encouraged to collaborate on existing, ongoing protocols rather than starting new, independent trials. New investigational agents may be added to the protocol over time as they become available or may be removed as deemed appropriate, using a platform trial approach, as described previously.[10] Special consideration should be given to allowing flexibility in the study sample size, since some assumptions, such as the case fatality rate in therapeutics trials, may need to be revised over time. In the context of public health emergencies in which there are substantial obstacles to developing reliable and meaningful evidence, we underscore the need for cooperation and coordination among research stakeholders, including funding agencies.[9] These types of large-scale, multipartner projects are logistically complex, but there is precedent for them in other areas of clinical research, such as in cancer clinical trials.[10] Given the effect of the ongoing Covid-19 pandemic, this message is especially timely. Core protocols are rapidly being developed by the WHO for trials assessing the efficacy of therapies and vaccines that are being developed to combat this infection. Implementing clinical trials for treatments during disease outbreaks under a core protocol could increase the chances of efficiently generating reliable evidence to determine which therapies are effective, thus providing timely information to public health officials and clinicians caring for patients.

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