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SUPPLEMENT ARTICLE

Operationalizing International Regulatory Standards in a Limited-Resource Setting During an Epidemic: The Sierra Leone Trial to Introduce a Vaccine Against Ebola (STRIVE) Experience

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International regulatory standards ensure human subjects protection, data quality, and scientific integrity of clinical trials. Operationalizing regulatory standards during a large vaccine clinical trial—the Sierra Leone Trial to Introduce a Vaccine Against Ebola—in a resource-constrained setting during an epidemic required flexibility and creativity. We highlight areas that required special attention, such as developing standard operating procedures appropriate for the setting, obtaining space and supplies for the regulatory office, and creating a strategy to maintain both a dedicated central regulatory office and satellite regulatory sites for this trial with paper-based records.

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The 2014–2016 Ebola virus disease (Ebola) outbreak in West Africa presented an urgent need for evaluation of Ebola vaccines in large-scale clinical trials. It was essential that these clinical trials, which, if successful, would be used as the basis for application for vaccine licensure, be conducted in compliance with international regulatory standards that ensure human subjects protection, data quality, and scientific integrity. The setting posed significant challenges, not only because the resource-limited countries highly affected by the epidemic had little previous clinical trial experience but also because of the time pressure and the social disruption caused by the epidemic.

The College of Medicine and Allied Health Sciences of the University of Sierra Leone, the Sierra Leone Ministry of Health and Sanitation, and the Centers for Disease Control and Prevention (CDC) began planning the phase II/III Sierra Leone Trial to Introduce a Vaccine Against Ebola (STRIVE) in October 2014. STRIVE began enrollment and vaccination in April 2015. The objective of STRIVE was to assess the efficacy and safety of the experimental Ebola vaccine rVSVΔG-ZEBOV-GP (Merck). STRIVE methods and results are described in detail elsewhere [1, 2]. In short, participants were healthcare workers or frontline Ebola response workers who were randomly assigned to receive either immediate (within 7 days) or deferred (18–24 weeks after enrollment) vaccination and were monitored for 6 months after enrollment and vaccination for adverse events and Ebola. The trial was unblinded; no placebo was used.

During the 6 months of preparation (a process that typically takes several years), ethical approvals were secured from the Sierra Leone Ethics and Scientific Review Committee and the CDC Institutional Review Board (IRB), and authorization was obtained from the Pharmacy Board of Sierra Leone (Sierra Leone's regulatory authority) and, under an investigational new drug application, the Food and Drug Administration (FDA). STRIVE was the first large vaccine trial to be conducted in Sierra Leone. The Pharmacy Board of Sierra Leone guidelines pertaining to vaccine clinical trials were newly updated (September 2014), and the standard timeline for processing clinical trial applications was specified as 60 working days [3]. However, given the time constraints created by the epidemic, ethical and regulatory reviews were conducted on an accelerated timeline so that STRIVE could be launched expeditiously. This was especially challenging because the study raised complex issues. For instance, the limited amount of data available on this vaccine made the selection and approval of a vaccine dosage more difficult than it would have been in a nonemergency vaccine development scenario. Firm ongoing commitment from all regulatory authorities to conduct reviews as rapidly as possible without compromising standards was essential. The STRIVE regulatory and implementation teams also very quickly developed procedures and documents, such as practices for maintenance of regulatory records and a manual of standard operating procedures (SOPs), that were both appropriate to the setting and compliant with international regulatory standards

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[2, 4]. Many of the facilities and standard processes available in most established clinical trial network sites were not available in Sierra Leone. Therefore, creating the regulatory structure for STRIVE required flexibility in typical SOPs to achieve compliance with the principles, regulations, and guidelines that ensure the integrity of clinical trials. This article describes some of the challenges and solutions in documentation of case histories, SOP development, office set up, and records maintenance and retention.

DOCUMENTATION OF CASE HISTORIES

Regulations, guidance, and accepted common practices [5–9] have been established to ensure scientific and ethical integrity of clinical trials. Often sponsors, investigators, and others involved in the design and conduct of clinical trials do not make the distinction between regulations, guidance, and accepted common practice in the development of SOPs and other aspects of trial conduct. As we planned for STRIVE, it was critical to bear in mind that typical standard practices might not be appropriate to the current setting and therefore might need to be modified, while maintaining thorough compliance with applicable regulations and guidance. Conducting a trial in an emergency in a resource-limited setting required a thorough understanding of ethical principles and quality regulations, open-mindedness regarding operations, and adequate time for discussion with stakeholders. This was challenging but possible, even when time was of the essence.

One example of the flexibility needed during STRIVE was the documentation of complete and accurate case histories. While FDA regulations [10] and the Pharmacy Board of Sierra Leone guidelines [3] require that investigators "prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation," the extent and type of material required to complete this documentation is not further elaborated. In many traditional clinical trial settings, medical records are extensive and are readily accessible by investigators. However, in STRIVE, medical records were often limited, incomplete, or difficult to access, owing to the epidemic and the setting. While vigorous effort was made to obtain and include all information from medical records, laboratory results, and other source documentation, in some instances the only available information was participant self-report of medical conditions and events. Since follow-up was conducted mainly by telephone, except when participants sought medical care, clinical observations by study staff were not routinely feasible. Therefore, study staff used case report forms to document participant descriptions of medical events more thoroughly than is done in a typical developed-country clinical trial setting. This practice had the added benefit of providing a snapshot of medical conditions in this population [11], for which few data had previously been available.

SOP DEVELOPMENT

Since the STRIVE sites were newly established and the majority of staff had no previous research experience, no preexisting institutional and departmental SOPs related to clinical trials were available on which to base STRIVE's SOPs. Typical SOPs generally describe various aspects of the execution of the study (eg, study visits, data management, dispensation of study product, and adverse event [AE] and serious AE reporting); STRIVE SOPs went further, though, to also include topics that would typically be outlined in institutional and departmental SOPs or policies, rather than in a study-specific SOP, such as handling media requests, how to communicate with the IRB, and details of implementation of ethical and confidentiality policies. In addition, STRIVE SOPs were more detailed and specific than usual SOPs, to avoid inconsistency across the sites. For instance, an SOP was written to explain how to complete data collection forms, from how to date a form to how to legibly write words and numbers, with examples of incorrect and correct methods.

FACILITIES AND SUPPLIES FOR A REGULATORY OFFICE

Practical challenges for STRIVE arose in setting up a regulatory office in Sierra Leone. Any clinical trial needs an office with basic supplies (eg, printers, scanners, lockable file cabinets, binders, and files). However, the immediate needs of the emergency response, which were appropriately prioritized over research, magnified the challenges of providing space and supplies for STRIVE. We thought we had found a solution by contracting with a local organization that had access to the necessary materials. However, even with this support, supply acquisition remained difficult. Local printing and office supply companies were overwhelmed, and supplies were often depleted, because many organizations needed similar supplies during the emergency response. Therefore, because printing locally was so difficult, regulatory documents that were more than a few pages long were printed in Atlanta, Georgia, and either shipped or transported by a CDC STRIVE staff member who was en route to Sierra Leone. Study supplies, such as file cabinets and file folders, were also imported in many instances. Curfews in effect during this time complicated delivery efforts. An awareness that office supply acquisition would require special attention could have eased some early difficulties in STRIVE implementation.

RECORDS MAINTENANCE AND RETENTION

In many clinical trials, each physical site is run separately under the supervision of individual-site-specific investigators who maintain their investigator site files within their respective sites. By contrast, the 7 STRIVE sites were all managed by a single local principal investigator and managing staff. These sites were located up to a 4-hour drive from the central regulatory office in Freetown, so satellite regulatory files were established within

enrollment and vaccination sites, participant follow-up sites, cold-chain depots, and laboratories, to facilitate the research staff's access to essential regulatory documents (eg, approved protocol and supporting documents, investigator brochure, participant screening and enrollment log, and vaccine accountability and dispensation logs). STRIVE had to use a paper-based file system because Internet access was unreliable in Sierra Leone. To minimize duplication while still ensuring ready access to these documents, careful consideration had to be given to which documents were stored at the satellite sites and which were transported to the central regulatory office. As sites and facilities closed when their work was done, careful planning was needed for collapsing the satellite regulatory files into the main investigator site files located at the central regulatory office in Freetown.

Finally, given the regulatory requirements [3, 6] for maintaining accurate and adequate records that are available for inspection, ensuring appropriate long-term storage of the files following study closure presented a logistical obstacle. Because there was no existing infrastructure in place for storing and ensuring the integrity of large numbers of paper files in Sierra Leone's hot and humid environmental conditions, a long-term storage facility to appropriately house the trial records had to be constructed. Refrigerated storage containers were repurposed to create a long-term storage compound by resting the containers atop a concrete base and equipping them with air conditioners, dehumidifiers, and electronic measuring and tracking equipment to ensure the maintenance of appropriate temperature and humidity levels. This facility was situated within a walled compound with a manned guard station to ensure security of the files.

CONCLUSION

In conclusion, creativity and flexibility were key to creating the regulatory structure for STRIVE, a phase II/III vaccine clinical trial that enrolled >8000 participants in the midst of the unprecedented Ebola epidemic in Sierra Leone. Time was always short because of the emergency, and the staff, procedures, and physical infrastructure for trial conduct all had to be built from the ground up. The trial design, consisting of multiple geographically diverse trial locations under the supervision of a single principal investigator, provided scientific benefits. However, it also posed challenges, such as coordination between sites. Ensuring proper documentation required ongoing thoughtful consideration of the requirements and available resources to ensure regulatory compliance.

Overcoming the operational, logistical, and conceptual challenges to meet the regulatory requirements for a high-quality clinical trial under difficult circumstances was accomplished by adhering to the underlying ethical and quality principles for clinical trials while exercising necessary and appropriate flexibility in development of SOPs and in meeting documentation and material requirements. The use of an electronic-based data collection system—with appropriate arrangements to ensure constant electricity and Internet access—instead of our paper-based system would have been more efficient and substantially reduced the short- and long-term storage requirements for a clinical trial. Because STRIVE was the first vaccine trial conducted in Sierra Leone, all SOPs were developed de novo. We hope that future trials will use our SOPs as templates and build on them to create a library of SOPs for ongoing use.

The regulatory capacity built during STRIVE has already been used in other clinical trials conducted in Sierra Leone. The STRIVE experience complements ongoing activities in Sierra Leone that are under the guidance of the African Vaccine Regulatory Forum (AVAREF) and aim to strengthen regulatory infrastructures for vaccine trials [12]. AVAREF was established in 2006 by the World Health Organization (WHO) to build regulatory capacity within participating countries by providing a forum to connect and promote communication between national regulatory authorities and ethics committees in countries within the WHO African Region, as well as in North America and Europe. In sum, the experience gained through STRIVE and the ongoing work of AVAREF have reinforced regulatory capacity in Sierra Leone and provide a foundation for future work in clinical research and public health.

Notes

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