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Development and Implementation of Clinical Trial Protocol Templates at the National Institute of Allergy and Infectious Diseases

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Abstract

Background: A clinical research protocol document must reflect both sound scientific rationale as well as local, national and, when applicable, international regulatory and human subject protections requirements. These requirements originate from a variety of sources, undergo frequent revision and are subject to interpretation. Tools to assist clinical investigators in the production of clinical protocols could facilitate navigating these requirements and ultimately increase the efficiency of clinical research.

Purpose: The National Institute of Allergy and Infectious Diseases (NIAID) developed templates for investigators to serve as the foundation for protocol development. These protocol templates are designed as tools to support investigators in developing clinical protocols.

Methods: NIAID established a series of working groups to determine how to improve its capacity to conduct clinical research more efficiently and effectively. The Protocol Template Working Group was convened to determine what protocol templates currently existed within NIAID and whether standard NIAID protocol templates should be produced. After review and assessment of existing protocol documents and requirements, the group reached consensus about required and optional content, determined the format and identified methods for distribution as well as education of investigators in the use of these templates.

Results: The templates were approved by the NIAID Executive Committee in 2006 and posted as part of the NIAID Clinical Research Toolkit[1] website for broad access. These documents require scheduled revisions to stay current with regulatory and policy changes.

Limitations: The structure of any clinical protocol template, whether comprehensive or specific to a particular study phase, setting or design, affects how it is used by investigators. Each structure presents its own set of advantages and disadvantages. While useful, protocol templates are not stand-alone tools for creating an optimal protocol document but must be complemented by institutional resources and support. Education and guidance of investigators in the appropriate use of templates

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is necessary to ensure a complete yet concise protocol document. Due to changing regulatory requirements, clinical protocol templates cannot become static but require frequent revisions.

Conclusions: Standard protocol templates that meet applicable regulations can be important tools to assist investigators in the effective conduct of clinical research, but they require dedicated resources and ongoing input from key stakeholders.

Keywords

Protocol; Template; Clinical Research; Standardization

Background

The National Institute of Allergy and Infectious Diseases (NIAID) is part of the National Institutes of Health (NIH), an agency of the United States Department of Health and Human Services (DHHS). NIAID funds research by both intramural and extramural investigators in a variety of settings ranging from single-investigator, single-site natural history studies to multi-center, international clinical trials ranging from Phase 0 through Phase IV. Regardless of the setting, in order to perform clinical research, a team led by a principal investigator must assemble a protocol document that is not only scientifically sound, but also is compliant with a range of regulatory, human subject safety and data quality requirements that undergo frequent revisions and are often subject to interpretation.

Regulations, policies and guidance on the conduct of clinical trials originate from multiple sources. Compliance with the Office of Human Research Protections (OHRP) Title 45 of United States Code of Federal Regulations (CFR) Part 46 [2] is required for NIH-funded clinical trials. When a clinical protocol involves an investigational drug, biologic or device, the protocol also must comply with the Food and Drug Administration regulations in Title 21 CFR [3]. NIAID Intramural research performed at the NIH Clinical Center also must adhere to NIAID Institutional Review Board (IRB) and NIH Clinical Center Medical Executive Committee policies. Extramural investigators must adhere to their state and institutional policies and procedures in addition to the NIH/NIAID terms of award for grants, cooperative agreements or contracts. International studies funded by the NIAID are required to adhere to the particular country's local research regulations and policies. In this complex regulatory environment, investigators are challenged with determining which regulations apply when overlap or conflicts between these authorities arise. Others have undertaken projects along the same lines as ours. Treweek et al. [4], for example, as part of the PRACTIHC Collaboration, have created tools for researchers with limited direct access to high-level professional resources to write trial protocols. They focus on “pragmatic” trials, referring among other things, to trials not intended for submission to drug regulatory agencies.

Each year, the NIAID holds a Winter Program Retreat to review the current state of research in the Institute. At the 2005 retreat, NIAID leadership expressed a concern that the process of writing protocols was an obstacle to the initiation of clinical trials across NIAID. First, investigators were finding it an increasing challenge to maintain current knowledge of required regulatory content for protocols. Second, a lack of standardized protocol structure presented a problem for investigators, especially those receiving funding for multiple NIAID projects with different templates for protocol writing. Although some of NIAID's three extramural and two intramural program divisions had existing templates and some research networks had network-specific templates, there had been no attempt to harmonize the content of the templates across the Institute. It was decided that an electronic protocol template, widely available via the internet, would assist investigators in writing and developing clinical trial protocols in compliance with regulatory and other requirements that would facilitate efficient review by NIAID reviewers [5,6]. Just as standardization efforts in health care increase uniformity of

practice and ultimately increase quality of care[7]; it was hoped that providing a standard tool for protocol development could facilitate harmonization of best practices throughout NIAID.

Methods

NIAID leadership approved the formation of the Protocol Template Working Group (PTWG) to develop a NIAID clinical protocol template as a priority project and charged the NIAID Clinical Research Subcommittee (NCRS) with its oversight. The mission of the NCRS is to improve the quality and efficiency of NIAID-sponsored clinical research through harmonization of policies and procedures across NIAID; to promote the exchange of best practices related to clinical research; and to disseminate information regarding clinical research resources. The PTWG assessed the current processes for protocol development across NIAID to develop a functional institute-wide protocol template.

Members of the Protocol Template Working Group represented all NIAID divisions that conduct or oversee clinical trials and included both intramural and extramural staff. Strengths of the working group process included: the members' collective experience in clinical trial design; clinical expertise in allergy and infectious diseases and a variety of perspectives on the content and structure of the template. Challenges that faced the working group process included: deciding the structure of the template; the number and type of the existing templates requiring review; reaching consensus on the core elements of the template and key language, such as definitions and safety reporting requirements. Programmatic differences and the varying perspectives of the working group members resulted in productive discussions leading to compromise on issues such as rectifying differences in protocol structure and developing a comprehensive template based on more than just study design, phase or setting.

The working group agreed that, at a minimum, the new template must comply with the requirements of International Conference on Harmonization (ICH) E6[8], but there was also agreement that the ICH E6 Table of Contents was not sufficient to meet the specific policy needs of the NIAID divisions. These NIH-specific policies included: the disposition of stored human subjects specimens and data, intramural and extramural publication policies, and the NIH policy for the inclusion of women and minorities as subjects in clinical research. The working group gathered the existing templates from each of the divisions, totaling 15 completed templates and five other templates in various stages of development. These documents were closely compared to one another, for programmatic specifications and to the ICH E6 Consolidated Good Clinical Practice Guidelines [8] and FDA 21 CFR [3] requirements for content and safety. The existing NIAID templates were found to comply with ICH E6 requirements, and met the needs of the current NIAID programs. Therefore, the existing templates remained unchanged and in force. However, new clinical trial networks and programs were still in need of a standard template that would not only incorporate the E6 and 21 CFR and 45 CFR 46[2] regulatory requirements but also outline trans-NIAID requirements.

Initially, the working group sought to create one template to satisfy both the intramural and extramural programs. However, the separate policy requirements of these programs drove the consensus away from a single template. For example, since the intramural program uses the NIAID IRB for protocol review, the intramural template would contain suggested language provided by the NIAID IRB whereas this language would likely not be accepted by all IRBs that review extramural research. As a result, separate intramural and extramural templates emerged. Despite the need to create two templates, a conscious effort at harmonization of core template structures and language was made to promote consistency of review by the Divisions, regardless of where the protocol was initiated.

The working group designed the templates to be used in both domestic and international clinical trials and for all phases of trials (i.e., Phase 0 through IV) rather than creating a series of templates to address individual settings and phases. One of the pre-existing NIAID templates [9], which was sufficiently comprehensive to meet the needs of most of the other Divisions, was chosen to serve as the backbone for the harmonized template sets. In order to maintain consistency, each template would be comprised of a shell document with a table of contents; section headings followed by both sample and required language, and place holders for appendices. Variation in intramural and extramural policy requirements necessitated the development of separate guidance documents with detailed instructions and discussions of key points, together with links to policies and regulations that could be valuable resources for both experienced and novice investigators and protocol reviewers. The draft templates were vetted by a variety of experts including medical officers, biostatisticians, safety and regulatory staff and the NIAID IRB to ensure accuracy and completeness.

Results

The NIAID Intramural and Extramural Clinical Trial Protocol Templates were first published in September 2006 as part of the NIAID Clinical Research Toolkit[1], an internet-based information repository for investigators. The working group recognized that, given the rapidly changing research environment both at the scientific and regulatory levels, ongoing resources for maintaining and updating the templates were required. Toward that end, NIAID appointed two staff, one from the intramural division and another from the extramural divisions, to serve as project leads, serve on the PTWG and provide ongoing support to the protocol templates. The project leads review policy and regulatory changes; solicit feedback from users and reviewers; promote the use of the templates; assist users with technical issues; maintain the template website page; convene working groups or subcommittees to conduct the annual review or to address specific issues; promote harmonization between the template sets as changes occur; vet changes through the appropriate experts; and report the status of the template sets to the NCRS on an annual basis.

Feedback from stakeholders and template users has also led to revision of the templates. For example, an Adverse Event Report Working Group was formed to assess the existing template language in the safety reporting section of the templates and come to consensus on new language for both templates. Feedback from intramural investigators and the NIAID IRB led to the development of an Intramural Natural History Protocol Template. This new template was developed because the use of the existing clinical trial template led to extraneous language, such as safety language on investigational agent exposure that was not relevant to the proposed natural history studies. A Stored Specimen and Data Analysis Template, driven by institutional policy changes, is being developed based on the structure of the standard protocol templates, again omitting any non-applicable elements.

To date, evaluations of the impact of these templates have been subjective. Intramural regulatory experts have noted that required and sample language embedded in the templates has contributed to development of more comprehensive protocol documents that expedited their review and approval. Because of the variability in content of clinical protocol documents submitted from the extramural community, regulatory experts from NIAID extramural programs have also commented that consistent use of the standard template could lead to more efficient reviews. Efforts are currently underway to gather objective data that measures the use of templates. One method is to quantify template website visits, which have increased five-fold over the last year (from 288 visits by December 2007 to 1807 visits by December 2008). However, these data do not indicate information about the site usage, such as user satisfaction. Measurements to assess the quality of the resulting protocols, such as decreased time to final approval, or reviewer opinions related to the increased efficiency of review, are underway.

Conclusions and Limitations

Regulatory and policy changes present a challenge as they drive modification of the templates. Figure 1 demonstrates that since January 2002, 98 policy, guidance, regulatory or procedural changes have affected protocol development at NIAID. Since new policies do not necessarily replace the old, they force continual assessment of the templates and often increase the volume of regulatory language required in protocols. In addition to added length, these policy changes or additions were noted to add complexity and interpretive challenges to protocol documents. For example, the recent OHRP guidance on the reporting of “Unanticipated Problems” [10] has differences in definitions and reporting requirements from the recent draft FDA “Guidance for Clinical Investigators, Sponsors and IRBs Adverse Event Reporting - Improving Human Subject Protection” [11], leaving investigators and institutions with the task of determining how to interpret the proposed changes. In addition, the FDA has issued 12 draft guidances and six proposed rule-makings that have been taken into consideration for their potential to affect template design and the inclusion of guidance and instructive materials. The protocol project leads have been careful not to incorporate draft guidance and instead to provide links to regulations rather than interpretation of those regulations, leaving that task to the institution and the investigators.

Despite the fact that the working group set out to write a single comprehensive template not driven by design, phase or setting, this was found to be impractical. The resulting templates do share a common structure and basic elements but a single template for all situations would not be adequate to serve the investigator community. Therefore, separate intramural and extramural templates were produced, and a Natural History Template evolved from user experience with the clinical trial templates. Although the templates can facilitate good clinical research, not all elements of the templates are appropriate for all phases of research or all settings. Investigators should therefore ensure that each protocol is comprehensive, yet contains only the appropriate template elements for their specific research. Likewise, reviewers are cautioned not to interpret the template as a checklist of mandatory content for all studies. Several examples of this occurred when the NIAID templates were first released and medical writers retained elements of the protocol template that were clearly not appropriate to the phase or design of the protocol.

It is important to note that, although templates can be applied to U.S. institutions conducting clinical research, because of the complexities of international trials, including the variability of regulations, policies and practices, templates for international studies may be difficult to standardize. Although templates can serve as a foundation and include ICH E6 requirements, the content must be geared toward the particular environment where the research is taking place and must reflect specific local requirements and policies.

In summary, when the decision is made to produce a common template, consensus must be reached on the core elements of the harmonized template. Additionally, programmatic differences among different parts of an organization drive compromises on the protocol structure. A protocol template has a lifecycle that includes assessment, vetting and maintenance phases, a process which is resource intensive. Templates should reflect a broad range of input from investigators, regulators and other stakeholders. Once templates are published for use, they demand long term stewardship to ensure that they are accurate and up to date with regulatory and policy revisions and they should be complemented by institutional support, review and oversight.

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Figure 1. indicates the interval and cumulative numbers of changes of policies and regulations that have occurred from January 2002 to March 2008, that have affected the language content in the clinical trial protocol templates.