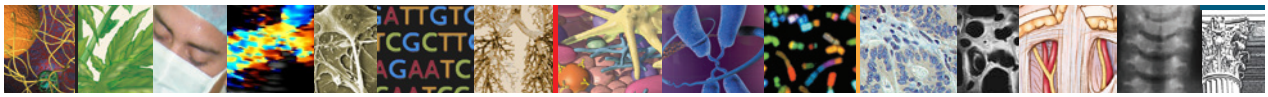

The NEW ENGLAND JOURNAL of MEDICINE

Perspective

Accreditation of Clinical Research Sites — Moving Forward

Greg Koski, Ph.D., M.D., Larry Kennedy, Ph.D., Mary F. Tobin, Ph.D., and Matthew Whalen, Ph.D.

Accreditation is used in many fields, including education, travel, construction, and health care. When implemented correctly, it improves quality, performance, and safety, while signaling to the public that an accredited entity is committed to an agreed-on set of values. Key to its effectiveness is broad acceptance of the standards on which it's based and a robust process for ensuring that accredited entities conform to them.

In clinical medical research, high-performing research sites are essential for the effective and efficient conduct of trials, but currently only a fraction of active sites would qualify as high-performing. There are a variety of potential solutions, including greater professionalism and voluntary accreditation.

Citing the many challenges facing the clinical trials endeavor and recognizing the lack of a reliable framework and method for assessing and ensuring research quality, Johnston et al. recently called for voluntary accreditation of clinical research sites to accelerate the dissemination of standards and processes and to accelerate development of therapeutic products.[1] Can the various players in the biomedical research-and-development ecosystem come together to implement accreditation that will be embraced by everyone involved as responsive to concerns about the operations and quality of research sites?

We submit that the answer is yes. In fact, approximately 6 years ago, an initiative to design a system of site accreditation was begun as part of a larger collaboration that aims to transform the clinical research process through the application of systems thinking — that is, seeing this complex endeavor as integrated sets of components (people, processes, and technologies) that are connected and interoperable, working together as a whole to achieve synergy.[2] Implicit in this initiative's conception was an understanding that an accreditation system must recognize and reward a site's commitment to high quality and performance and that sites and trial sponsors would have to be compensated somehow for the burden of achieving such accreditation. Today, this initiative is coming to fruition, and we believe that it will soon provide the essential elements of an effective program for accreditation of clinical research sites.

The initiative followed a consensus approach (see box).[3] The first step was a broad-based survey of relevant parties to elicit their attitudes and opinions regarding the characteristics of high-performing research sites, the sorts of standards whose application could engender those characteristics, and the challenges involved in adopting both standards and accreditation processes.[4] These insights provided the basis for a multiyear effort to create standards that

Principles for Developing Standards.*

Independence
Maintain standard development as an independent activity
Collaborate, harmonize, and integrate to avoid duplication
Establish a management team
Use standards experts for writing

Transparency
Disclose and manage potential conflicts of interest
Publish methods and publicize ways in which to participate in the development of standards
Create an open process for stakeholders and the public to review draft standards

Effectiveness
Organize separate domain work groups
Stakeholders nominate small group of experts to draft standards
Standards are based on public comments from stakeholders
Use a common template to describe standards
Work virtually to expand participation
Develop methods to assess the value of standards to the research ecosystem

*Adapted from Johnston et al.[3]

would benefit clinical trial participants, competent authorities, institutional review boards, and the public.

Next came development of an overarching initial set of standards focused on overall quality management. Diverse working groups convened by the nonprofit Alliance for Clinical Research Excellence and Safety (ACRES) have worked over the past 2 years in conjunction with the British Standards Institution to develop such a set of standards. We initially focused on quality management, with the aim of protecting the rights and well-being of research participants and facilitating clinical trial results that are verifiable, valued, and valuable. This effort has been grounded in a conviction that quality is an essential element of any process-improvement initiative, including accreditation.

These quality standards are now being made available by request to qualified individuals and organizations for review and comment as part of an ongoing consultation, development, and validation process (https://standardsdevelopment.bsigroup.com/Projects/9018-01652).[5] They incorporate some well-established and generally accepted standards and applicable guidelines, such as those issued by the International Organization for Standardization (ISO) and the International Council for Harmonization (ICH). And they provide a foundation on which more specific standards will be developed for multiple domains (e.g., facilities, personnel, information technology, management and administration, and patient engagement). These domain-focused standards will be incorporated in future years, as the accreditation process evolves. Certain specialized standards are also planned for areas such as pediatric trials, first-in-human studies, and studies in cognitively impaired people.

Standards alone cannot be effective without a robust accreditation process. As currently envisioned, a process that progresses from commitment to achieving accreditation, to assessment of performance and quality, through qualification for and maintenance of accreditation will permit a staged implementation that can accommodate the wide variation in readiness among existing sites, without imposing an undue burden on individual sites. The standards developers recognize that such flexibility is essential to the effectiveness of the process. Furthermore, the process itself must not create a barrier to participation, but rather must constitute a program with incentives for progressive improvement through which sites can demonstrate and be rewarded for their commitment to excellence in performance.

In their call to action, Johnston et al. speak to the need for standards that will promote both quality and efficiency, but they focus on metrics.[1] Metrics are necessary for assessing performance and quality, but like guidelines and standard operating procedures, they should not be confused with formal standards. Although typical "standards" language, such as that in the ICH Good Clinical Practice Guidelines, often clearly indicates what must be done, it generally does not clarify the rationale in a way that ignites and maintains a workforce's motivation, nor does it outline the process whereby required competencies can be developed or improved.

Similarly, since there have previously been no true standards for clinical research sites, calls for "harmonization of standards"[3] could result in an overemphasis on performance metrics and measures of compliance. An emphasis on creating a culture of competence and conscience that produces compliance and responsible performance relevant to trial requirements and patients' needs is more in the spirit of true standards and robust accreditation. The effort to develop global accreditation for clinical research sites brings together representatives of the various parties engaged

in the research enterprise and harnesses their expertise and investments to collaboratively respond to this challenge so that all the relevant needs are addressed.

The question of who will do the accrediting remains under consideration. Since the accreditation process must be objective and free from potentially conflicting financial interests, we envision the creation of an independent entity to house and maintain the standards. The accrediting bodies will probably include nonprofit public-interest organizations, for-profit organizations, and government agencies (depending on the prevailing norms in individual countries), but each organization should be approved by the independent entity to ensure fair and consistent interpretation and application of the standards globally.

Experience with existing accreditation programs calls into question the viability and practicality of relying solely on site visits for assessing suitability for accreditation. Instead, a combination of guided self-appraisals leveraged by judiciously conducted on-site assessments and the liberal use of user-friendly supporting technologies (such as video conferencing, electronic clinical trial management systems, and distributed network collaboration platforms) by site personnel will be essential. Equally challenging to traditional accreditation models is the sobering reality that more than 100,000 research sites globally will probably have to be accredited (and yet more are emerging in response to the evolution of personalized and precision medicine). Accommodating all these sites involves substantial logistic challenges that cannot be overcome without innovative approaches. The most important of these is deployment of technology for information exchange and validation by trial sponsors, contract research organizations, patients, regulators, and researchers to achieve a technology-assisted dynamic accreditation process.

Key to implementation of site accreditation will be acceptance and recognition of its value by all these players. As we continue to develop the accreditation process, including addressing important financial considerations and implementation methods, we recognize that the process must be practical and sustainable and that perspectives from all stakeholder groups are essential. With the initial global quality standards now available, a pilot implementation program is slated to begin in early 2019. We believe this effort is long overdue, but it's not too late to move it forward.

Disclosure forms provided by the authors are available at NEJM.org.

From the Alliance for Clinical Research Excellence and Safety, Cambridge, MA.

This article was published on June 27, 2018, at NEJM.org.

1. Johnston SC, Austin CP, Lewis-Hall F. Voluntary site accreditation — improving the execution of multicenter clinical trials. N Engl J Med 2017;377:1414-5.
2. Koski G, Tobin MF, Whalen M. The synergy of the whole: building a global system for clinical trials to accelerate medicines development. Clin Ther 2014;36:1356-70.
3. Johnston SC, Lewis-Hall F, Bajpai A, et al. It's time to harmonize clinical trial site standards: discussion paper. Washington, DC: National Academy of Medicine, 2017 (https://nam.edu/its-time-to-harmonize-clinical-trial-site-standards).
4. Bajpai A, Koski G, Tobin M. Aiming high. International clinical trials. London: Samedan, 2015 (http://www.samedanltd.com/magazine/13/issue/238/article/4149).
5. ACRES-QC S001 ACRES quality continuum standard for the quality management of clinical research sites. BSI standards development. London: British Standards Institution (https://standardsdevelopment.bsigroup.com/).

DOI: 10.1056/NEJMp1806934