It’s Time to Harmonize Clinical Trial Site Standards

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ABSTRACT | Climbing costs and lengthy time frames of clinical trials are significant bottlenecks in medical product development. Despite the fact that scientific discoveries yield many new possible targets for developing into therapies, the capacity and resources with which to develop these targets are limited, thereby leaving potentially valuable discoveries undeveloped and unrealized. Under the aegis of the Clinical Trial Site Standards Harmonization Action Collaborative (“the Collaborative”) of the Forum on Drug Discovery, Development, and Translation of the National Academies of Sciences, Engineering, and Medicine, clinical research stakeholders set out to discuss opportunities to improve clinical trial site functioning, with the goal of increasing productivity in medical product development. Our conclusion: harmonization of standards for clinical trial sites has significant promise in improving clinical trials. Standards would also be essential to the formation of a site accreditation system in the United States, should a consensus emerge on the need for such a system. This paper synthesizes the results of the work conducted to inform discussions of the Collaborative. This paper may serve as a launching point for harmonizing requirements applied to clinical trial sites and the development of standards. A clinical trial infrastructure that reduces redundancies and increases efficiencies would, in turn, accelerate the pace and productivity of new product development, to the benefit of patients and society.

Investing More, Producing Less

Patients are in need of new medicines to treat an array of rare, common, and complex diseases. By its nature, the development of a new medicine, vaccine, device, or diagnostic is a careful process, one executed in keeping with the cardinal rule of medicine: “First, do no harm.” Today, however, biopharmaceutical development faces an efficiency crisis, and the stakes for reform are high. Without a substantial increase in the rate of clinical success and subsequent drug approvals, many observers believe innovators will be unable to bring forward enough new medicines to sustain investment in research and development (R&D) activities [1]. The costs of development have skyrocketed, but...
productivity has lagged. There are numerous reasons for this growing gap in efficiency, including the reality that biomedical R&D is increasingly centered on highly complex, poorly understood disease states such as Alzheimer’s.

Across therapeutic areas, the biopharmaceutical development process itself is rife with inefficiency. In a world at ease with mass customization, biopharmaceutical development remains largely a realm of isolated “one-off” clinical trials with redundancy and far less interoperability and adoption of best practices than might be expected [2]. In a given multicenter trial, 11 percent of sites fail to enroll a single patient, 37 percent of sites do not meet enrollment targets, and studies are typically lengthened (often to double the original timeline) to satisfy enrollment targets [3]—thereby constituting a significant use of resources to launch clinical trials that fail or struggle to reach the desired return on that investment.

Major scientific, technical, and commercial management advances in the past 60 years hold the potential to transform drug development, but innovators have been unable to keep pace. The term Eroom’s Law (the antithesis of Moore's Law, describing ever-rising computing power) has been coined to reflect the reality that drug discovery has become slower and more expensive over time despite efforts by drug developers to improve productivity. The number of new drug approvals each year has remained relatively flat since the 1950s, but the cost of developing a new drug has doubled approximately every nine years, and overall R&D spending continues to increase [4]. Experts cite the formidable challenges and high costs associated with clinical trials—research studies that rely on hundreds or even thousands of volunteer research participants to help test whether drug products are safe and effective—as driving this negative trend and creating a persistent bottleneck in the drug development process [2,5,6].

Although the number of new compounds in development has increased over time, the high cost of clinical trials remains a challenge because of a number of factors, including ever-increasing time and financial pressures on clinician-investigators, excessively risk-averse interpretations of regional and federal regulations, the increased complexity of clinical trial protocols, and the high cost of on-site clinical data-quality monitoring (often including 100 percent source document verification—the practice of comparing each data point entered in a clinical trial with information from the primary health records of a trial participant). An additional factor: the accumulation of local, regional, national, and international regulations, often developed in reaction to specific issues but rarely accompanied by thoughtful streamlining, sunsetting, or harmonization [7,8].

There are also challenges in the core capabilities of clinical trial sites, such as contract negotiation and institutional review time frames, study start-up, patient recruitment, and the completeness and quality of research data [9]. The ways in which standards for protecting research participants are applied are often significantly different. Processes for consent and adherence to good clinical practice guidelines are suboptimal at some sites, and standards for training and site-level preparedness are neither widely agreed upon nor consistently applied [10]. The consequences of fragmented, often duplicative systems are borne by research participants, investigators, innovators (including the National Institutes of Health [NIH]), academia, foundations, and the biopharmaceutical industry. The most serious consequences are borne by research participants, and ultimately patients, awaiting potential new therapies that never complete the clinical trial process or are never tested clinically.

Value Proposition for Harmonization

Beginning in 2012, participants in the Collaborative began exploring ways to improve the efficiency of the clinical trial process. Initial discussions focused on the feasibility, benefits, costs, and risks of developing a fully formed accreditation system for clinical trial site performance, and forging a planning framework for such an accreditation process. Extensive face-to-face meetings of the Collaborative were held in December 2012, August 2013, and March 2014, with teams working in small groups between meetings.

Discussions focused on the feasibility of clinical trial site accreditation, based on other models in the health care industry. Some of these models are quite robust, because the concept of voluntary, continuous performance improvement systems for health care organizations has a long history in the United States. Regulations—rules that must be followed and rules having the force of law—issued by the US Food and Drug Administration (FDA), it can be argued, are designed to raise the performance of all parties in biopharmaceuticals to an acceptable (and enforceable) standard. Along with
FDA regulations, voluntary accreditation has emerged as a route by which to certify adherence to processes consistent with success and as a high-profile “seal of approval.” Such certification and recognition would allow pharmaceutical companies and other research sponsors to contract with accredited clinical research sites with some degree of confidence in performance expectations, without the need to conduct audits for each clinical trial.

In the United States, the best-known health care accreditation process focuses on hospitals. Studies have shown that certification by perhaps the best-known accrediting organization of hospitals, The Joint Commission, is a key predictor of effectiveness in patient safety [11]. Accredited trauma centers have demonstrated significant reductions in patient mortality [12]. For acute myocardial infarction, hospitals that were not surveyed or accredited had lower performance on care related to that condition, as well as higher mortality rates, than those that were accredited [13]. Since the Clinical Laboratory Improvement Amendments (CLIA) of 1988 established quality standards for all nonresearch laboratory testing performed on human specimens, federal government data indicate that CLIA has improved the quality of lab testing in the United States, with one indicator being a 40 percent reduction in laboratory quality deficiencies [14].

A voluntary system of accreditation of clinical trial sites could include the following benefits:

• For clinical trial sites, voluntary accreditation could provide consistent and transparent application of baseline standards for core competencies, reduced administrative burden, recognition for high-quality performance, and a competitive edge. “Add-on” certification options beyond baseline accreditation could attest to a clinical trial site’s unique expertise and ability to conduct research in a particular therapeutic area or patient population.

• For research participants, voluntary accreditation could provide greater confidence in the quality of clinical trials conducted at accredited sites. Such confidence could help encourage volunteers to participate in clinical trials, thus improving treatment options in the future.

• For research sponsors, the consistent and transparent application of clinical trial site standards in an accreditation system could allow for easier identification of high-quality sites for various types of studies, faster study start-up, and a reduction in the administrative burden from conducting repetitive site evaluations.

• For regulators of clinical research, an accreditation program could provide greater reliability of—and confidence in—the evidence generated for a medical product.

The value proposition for clinical trial site standards and/or accreditation has already taken hold in several emerging clinical research markets. China and South Korea, two of the fastest-growing international clinical trial markets, now have the infrastructure to support accreditation systems for clinical trials [15,16]. India’s government has also mandated quality accreditation of new clinical trials to build trust in that nation’s clinical trial industry [17]. A new Clinical Trials Regulation became effective throughout the European Union starting in May 2016 and may set the stage for harmonized clinical trial procedures conducive to the establishment of an international accreditation system [18].

Given these advantages, why not move to accreditation in the United States right now? First, achieving and maintaining accreditation status requires a significant investment of resources and would be initially time consuming for investigators. There may be a question about whether accreditation is worth the time, effort, and cost. Accreditation may also be a barrier to those who have the skill and desire to serve as investigators for certain specialties but not the time and resources to hurdle the accreditation bar. In addition, the standards underpinning accreditation might be challenging and time consuming to develop and/or revise, thereby having the potential to diminish the efficiency that could be achieved through an accreditation process.

Although improvements in the transparency, harmonization, and adherence to “best practices” for clinical trial sites would benefit the efficiency and quality of clinical trials, moving to an accreditation system may not be realistic at this time. Development of standards would be a prerequisite for any staged accreditation process. Given this reality, participants in the Collaborative reserved the option of accreditation in the future but shifted focus to what would be the core operation of any potential accreditation body—the creation and maintenance of standards for clinical trial sites.
Setting Standards: Fundamental to Improving Clinical Trials

Standards are a fundamental building block in a modern society. Electronics, automobiles, home appliances, and many other products and systems that surround us are engineered and built to satisfy accepted standards. Standards are also used to establish expectations on quality and performance. For example, commercial aircraft pilots around the world use a standard preflight checklist to make certain that an airliner is fit to fly.

The need for standards around processes and performance is clear. Different sponsors, including contract research organizations (CROs), often impose myriad requirements on clinical trial sites. Expectations for clinical trial site performance may vary by sponsor, and even within a single sponsor. Verifying the quality of the research being conducted at a site means multiple and often duplicative on-site visits. These can be time consuming and costly, accounting for 25 to 30 percent of the cost of conducting a trial [19], yet there is no evidence that this level of on-site monitoring improves outcomes [20]. Increasing consistency in clinical trial initiation and execution could reduce costs, increase data integrity, speed development, and better serve research participants [21,22].

One example of a bottleneck caused, in part, by a lack of standards is trial delay associated with study start-up, including institutional review board (IRB) consideration of clinical trial protocols. IRBs play a crucial role in protecting research participants, but they differ in the application and interpretation of the same federal regulations and in judgments made about risks to research participants [23]. The time taken to complete IRB review also varies substantially.

IRB review is just one aspect of the study start-up and business operations processes for clinical trials that could benefit from standard measures of efficiency [24]. Other approaches, such as monitoring checklists and quality assurance procedures, could be standardized by research sponsors, regulators, or clinical trial sites themselves to ensure that clinical trials are implemented as designed, regulations governing the conduct of clinical trials are followed, and data used to assess treatment effects are valid. These are important opportunities to assure the efficiency and quality of clinical trial procedures. High-integrity, well-executed clinical trials establish strong protections for patient volunteers while generating reliable evidence to determine the answer to the question being asked in the trial [20].

It is worth noting, however, that harmonizing the conduct of clinical trials will not solve all challenges facing them. Sponsors play an important role in the efficiency of clinical trials. For instance, sponsors have the opportunity to provide thoughtful reviews of clinical trial protocols as they are being developed to ensure that unnecessary complexity is not built into the trial. Complexity, particularly in the form of adding painful or invasive procedures, can drive down interest and enrollment in trials.

Moving Forward through Collaboration

In discussions, it became clear that research sponsors want better ways to identify high-performing clinical trial sites. Sites, in turn, need and want to know the definition of quality and how best to implement change within their organizations to meet sponsor expectations. Moreover, work has been going on for some time on standards for clinical trial sites. Organizations such as TransCelerate and the Society for Clinical Research Sites have already developed site-qualification and training tools to facilitate mutual recognition of certain investigator and site capabilities across some companies [25]. The Alliance for Clinical Research Excellence and Safety (ACRES) has also embarked on an international stakeholder consensus process of creating global standards for accreditation of research sites (the Site Accreditation and Standards Initiative) [26,27]. Some sites are also willing to share performance data to provide a benchmark against their peers and facilitate recognition for excellent performance. Overall, opportunities now exist for a broader collaboration of clinical research stakeholders, including clinical trial sites, to

- collect and analyze requirements applied to research sites by sponsors;
- identify and prioritize requirements associated with positive performance and productivity to aid in the recognition of best practices and prevent proliferation of ineffective standards;
- evaluate existing site requirements—such as those from the organizations mentioned above—and assess their potential for broader application;
- harmonize, publicly share, and pilot the application of common requirements across clinical trial sites used by research sponsors;
participating in this effort; and
- iterate and refine requirements based on a scientific method as a precursor to developing standards.

An alliance of research sponsors working in partnership with clinical trial sites and other experts in this area could be well suited to conducting this work. The initial goal: operational-level clinical trial site standards that would apply to any site regardless of size or therapeutic expertise. The next step could then be developing more complete standards that should apply to specific therapeutic research areas or populations.

Developing a Framework for Standards

Standards for clinical trial sites should identify the requirements to safely conduct clinical research, enhance the protection of research participants, promote the measurement and improvement of performance over time, and increase the efficiency of sites. Several Collaborative participants convened a working group to envision a framework for standards. The group’s initial focus was on discussing a framework for developing standards in the context of a system that may eventually lead to accreditation. However, the principles suggested by the group apply to any effort to develop standards.

For the purpose of developing standards, this working group suggested that a clinical trial site be defined as a physical area or areas designated for activities necessary to conduct clinical research. Notably, a site would include an investigator and a physical address where research activities are conducted. Specificity is needed, because sites such as academic institutions may have many investigators at one physical location or spread across a number of locations.

Over time, additional standards may be used to evaluate clinical trial site performance for various types of specialized research and may be tiered based on risk to research participants, protocol complexity, and required resources and capabilities. Specialized categories of standards may also be developed to apply to

1. type of study,
2. type of intervention, and
3. patient populations or conditions being treated.

### Box 1 | 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.

**Transparency**
- Disclose and manage potential conflicts of interests.
- 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.
  - Finalize standards based on public comments from stakeholders.
- Use a standard template to describe standards.
- Work virtually.
- Develop methods to assess the value of standards to the research ecosystem.

Basic principles suggested by the working group to guide the process for developing standards are outlined in Box 1.

Seven performance domains for standards, with related subdomains, were also suggested by a working group of the Collaborative for the initial assessment of current standards applied to clinical trial sites and piloting initial harmonized standards (see Figure 1 below). Overarching metrics for the domains and subdomains listed below are the efficiency and speed of the processes required to initiate and complete a clinical trial (e.g., time to IRB approval, contract completion, research participant recruitment rate versus goal).

The working group suggested that domain experts consider the following goals for developing the standards themselves:

**Evolution**
- Harmonize and integrate existing requirements; identify gaps.
- Develop a starter set of standards and evolve with experience.
- Focus first on the United States, but consider and align with global standards where possible.

**Definition**
- Define a common template for standards.

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**Figure 1 | Performance Domains and Subdomains for Clinical Trial Site Standards**

• Develop realistic standards that are not beholden to ideals.
• Base standards on evidence, when possible.
• Focus on metrics that seek a high standard of quality, not merely standardization.
• Recognize tiers, types, and so on for sites to differentiate.
• Specify degree of intended enforcement, with standard words such as must, shall, should, may.
• Separate umbrella organization standards.
• Differentiate process and practice from performance.
• Describe conformance and evaluation measures.

**Next Steps**

Based on a review of the evidence and discussions as part of the Clinical Trial Site Standards Harmonization Action Collaborative, there may be an opportunity to convene clinical trial stakeholders in a neutral setting to harmonize requirements applied to clinical trial sites. Harmonization is a worthy goal unto itself and essential whether or not the stakeholders in clinical trials move to an accreditation process.

As a next step, several participants in the Collaborative have begun a project to collect, analyze, and assess how the clinical trial site requirements applied by research sponsors (academia, NIH, biopharmaceutical companies, CROs) could be harmonized. The project involves analysis of information (e.g., site selection and monitoring checklists) from participating research sponsors organized by the initial performance domains and subdomains suggested in Figure 1. The analysis intends to identify requirements that are

1. the same among a subgroup of research sponsors,
2. not the same but may be equivalent, or
3. clearly different or used only by some sponsors in the subgroup.

Aligning and defining the most common elements of the clinical trial site requirements currently in use would provide a foundation for harmonization. The project will serve as the foundation for identifying baseline standards that research sponsors could apply broadly to clinical trial sites. This approach could position the clinical trials enterprise to develop standard measures of efficiency for clinical trial performance and accelerate systemic reforms [22]. The authors invite interested parties to join with them to achieve this goal.

In summary, improving the efficiency of clinical research, and biomedical research and development more broadly, and reducing the time and financial costs of this research for all those with a stake in the process will benefit everyone, especially patients awaiting new therapies. Changes need to produce net benefits. Harmonization is the next step. Decisions about future goals—including accreditation—can be made after the development, adoption, and evaluation of harmonized standards. In that way, stakeholders in the highly complex world of clinical trials can ensure that changes will have the predicted real-world effects, and that a solid foundation is in place for continuous further improvement.

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