Expert Commentary

Clinical Trials: Rethinking How We Ensure Quality

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Martin Landray is a member of the Clinical Trials Transformation Initiative (CTTI) Steering Committee, a public-private partnership cofounded by Duke University and the FDA, and was a team leader for CTTI's Monitoring Project. He was also a member of the Risk Stratification Subgroup of the UK Medical Research Council/Department of Health/Medicines and Healthcare Products Regulatory Agency Joint Project Risk-adapted Approaches to the Management of Clinical Trials of Investigational Medicinal Products. Dr. Landray works at the University of Oxford Clinical Trial Service Unit & Epidemiological Studies Unit (CTSU). CTSU conducts large-scale clinical trials (particularly in cardiovascular disease, renal disease, diabetes, and cancer) and receives research funding from government, charity, and the pharmaceutical industry. Dr. Landray complies fully with the CTSU staff policy of not accepting payments (including honoraria and speaker fees) from or holding stocks in pharmaceutical, tobacco, or alcohol companies (although travel and subsistence costs may be reimbursed).

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INTRODUCTION

Concern is widespread that clinical trials are becoming increasingly costly and burdensome to conduct.[1] The challenge is to find efficient and practical means of ensuring that trials provide conclusive answers while safeguarding the well-being of the patients who take part in them. Monitoring—often via site visits, post-hoc data checks, and site auditing—is used to assess compliance with the protocol to ensure the safety of patients and the reliability of results. For trials that enroll large numbers of patients in multiple sites and multiple countries, the logistical and financial implications of frequent monitoring visits are daunting and are prohibitive for trials based in community or other routine health care settings. Furthermore, auditing a trial after patients are enrolled and data have been collected may not be the most efficient or effective means to ensure optimal human subject protection and trial quality. Accordingly, many in the clinical trial enterprise have expressed concerns about whether the current model for monitoring trials is effective and should be sustained.

Parallels have been drawn to similar issues confronted by the pharmaceutical manufacturing sector in ensuring product quality. In response to the challenges posed by increased numbers of domestic and foreign facilities and greater diversity and complexity of drugs and manufacturing processes, the U.S. Food and Drug Administration (FDA) launched a risk-based quality initiative, "Pharmaceutical Quality for the 21st Century,"[2] which relies on "quality by design" (QbD). This approach posits that manufacturers identify critical process control points that substantially affect product quality and institute prospective measures to monitor the product at those points.[2,3] Detection of unacceptable variation allows corrections to be made that will re-establish product quality. This initiative gives oversight of critical parameters and product quality to drug manufacturers, while the FDA initially ascertains that

critical process control points have been identified and will be monitored appropriately and subsequently conducts selective inspections.

A NEW PARADIGM—QUALITY BY DESIGN FOR CLINICAL TRIALS

A QbD model can be envisioned for clinical trials whereby those responsible for the overall conduct of a trial would identify the critical aspects that, if not performed correctly, would threaten the protection of patients or the integrity of results. Those critical indicators of trial quality would be assessed on an ongoing basis so that corrective actions can be made early. In this context, trial quality is defined as the avoidance of errors that matter to decision-making, and monitoring is repositioned as a tool for evaluation and improvement.[4]

Applying the QbD approach to clinical research, those responsible for the overall conduct of a trial would ensure that a quality management plan has been developed alongside the protocol and before trial initiation. Ideally sponsors, regulators, and investigators would agree with the plan before the study begins, thus reassuring all parties that an appropriate approach is being taken to ensure trial quality prospectively.

In a workflow similar to the Plan-Do-Check-Act schema in widespread use in quality improvement programs (Figure), the protocol ("**Plan**") should be carefully designed and articulated, and should clearly assess key risks to human subject protection and reliability of the results. The clinical trial sponsor should assess the degree of tolerance for errors or deviations in performance, establish methods for minimizing important errors, and describe metrics for assessing them. Tolerance for errors may differ depending on the intervention under study (e.g., the stage of development, previous experience), the patient population, and the trial design (e.g., the size of the trial and the presence of a randomized comparison). This forward planning gives

focus to the operations ("**Do**") so that the sponsor gives relevant training to and deploys appropriate personnel, designs systems to meet protocol requirements, and tailors procedures and operations to maintain quality.

Monitoring ("**Check**") should likewise be focused, selecting methods that are effective in detecting errors that will significantly affect quality, rather than simply using methods because they are "standard practice." The approach should be targeted to the protocol, encompassing the full range of risks, and may use multiple strategies, such as trial steering and data monitoring committees, pharmacovigilance and clinical oversight, central or statistical methods, and on-site visits. Importantly, this oversight should form part of a quality improvement feedback loop ("**Act**") in which the sponsor reviews findings, modifies the risk assessment, and makes changes to all relevant components of the cycle, including the protocol, trial procedures, and monitoring, as appropriate.

Throughout this framework of assessing and managing risks to quality, it is important to focus on those aspects that are of greatest importance, recognizing the opportunity costs of being distracted by activities that do not significantly affect subject safety or data quality. The risk assessment must consider the likelihood of errors occurring in key aspects of study performance and the anticipated effect of such errors on human subject protection and the reliability of the trial results. For example, risks to human subject protection are generally greater in trials that involve relatively untested interventions, invasive procedures, or vulnerable populations. Such risks must be mitigated and monitored appropriately. In large randomized controlled trials, errors that are random with respect to treatment allocation, such as errors in measurements and dates or use of unadjudicated outcomes, may increase the likelihood of finding no difference where one might in truth exist, but do not bias the conclusions in favor of any one treatment arm. By

contrast, systematic errors (i.e., those that are more frequent in one treatment arm than another) are of much greater concern. Examples include more intensive follow-up or medical management in one group than the other, or premature termination of follow-up in patients at the time of a first study outcome or when study treatment has been stopped.

MAKING THE TRANSFORMATION

The Clinical Trials Transformation Initiative (CTTI), a public–private partnership founded by the FDA and Duke University, has assessed the role of monitoring as a component of quality in clinical trials and announced its recommendations in May 2011.[4] These recommendations put QbD at the forefront of the clinical trial process (Table). Crucially, they do not advocate additional layers of regulation or bureaucracy but encourage a thoughtful restructuring of existing practices, emphasizing careful planning and streamlined execution.

The CTTI monitoring initiative included participation from U.S. and E.U. regulators, and further efforts are underway to encourage widespread adoption of the recommendations. Notably, the FDA recently issued draft guidance on risk-based approaches to monitoring clinical trials.[5] This guidance describes monitoring strategies that reflect a modern, risk-based approach focusing on critical study parameters and relying on a combination of monitoring activities to oversee a study effectively. Key to future success will be the development and exchange of knowledge and experience of different quality management systems applied to clinical trials, including the role of different approaches to monitoring.

Successful transformation of the clinical research enterprise will require greater collaboration both within and across sectors of the clinical research enterprise, including collaboration among those who fund, design, conduct, participate in, and regulate clinical trials,

as well as those who use the results for health care decision-making. The message is simple: quality must be built into the very fabric of a clinical trial. There must be a focus on key risks with objective assessment of critical aspects of performance. We believe that the proposed QbD approach will enhance human subject protection and increase the reliability of trial results, to the benefit of study participants and future patients.

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FIGURE. Quality by design: a new paradigm for ensuring quality in clinical trials

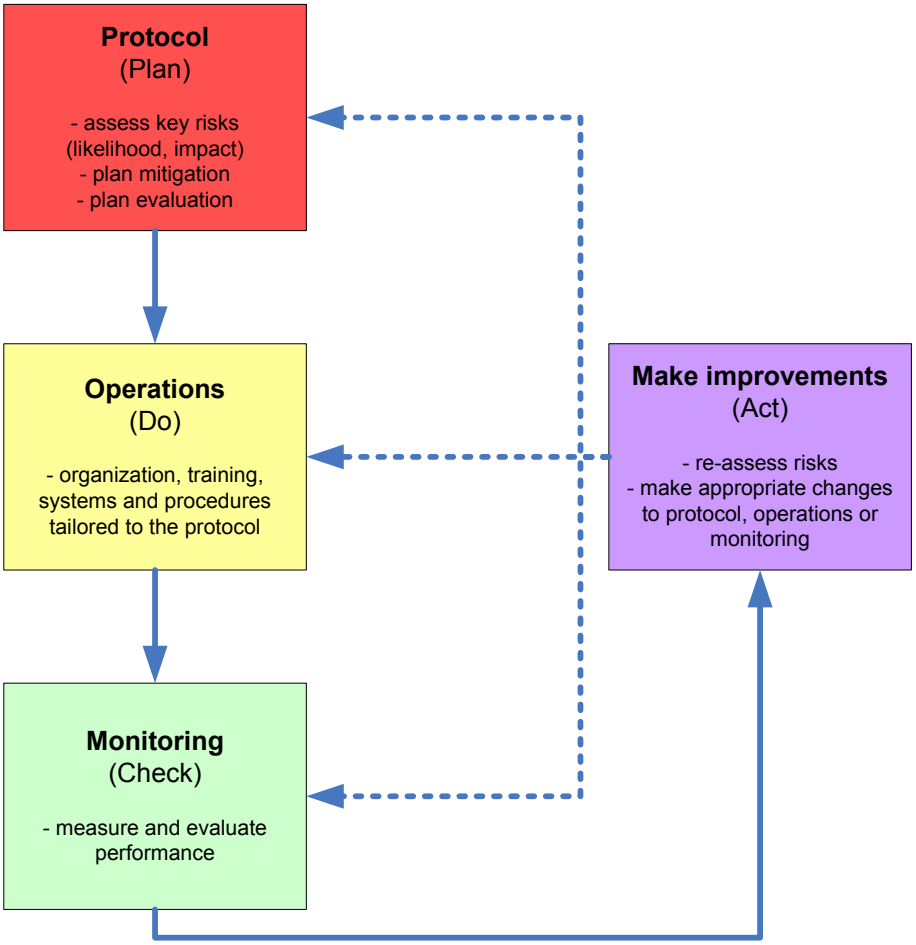

TABLE. Clinical Trials Transformation Initiative recommendations[4]

Primary recommendation: **Build quality into the scientific and operational design and conduct of clinical trials**
■ **Focus on what matters** ◆ "Quality" is defined as the absence of errors that matter (i.e., errors that have a meaningful impact on patient safety or interpretation of results) ◆ Determine what matters for the specific trial ■ **Develop a quality management plan** ◆ Initiate plan in parallel with protocol development ◆ Focus on areas of highest risk for generating errors that matter ◆ Seek regulatory review of plan ■ **Assess performance in important parameters** ◆ Prospectively measure error rates of important parameters ◆ Tailor monitoring approach (e.g., site visits, central, statistical) to the trial design and key quality objectives ■ **Improve training and procedures** ◆ Base on measured parameters ■ **Report findings of quality management approach** ◆ Include issues found, actions taken, impact on analysis and interpretation of results ◆ Incorporate into regulatory submissions and publications ◆ Encourage inclusion in International Committee of Medical Journal Editors requirements
Ancillary recommendations
■ **Share knowledge and experience** ◆ Collaborate among academia, industry, and regulators to share methodologies and data ■ **Encourage appropriate regulatory guidance** ◆ Emphasize key principles of quality trials (i.e., human subject protection, reliable results, protocol adherence) ◆ Encourage risk-focused oversight of trials ■ **Promote education and awareness** ◆ Focus on those involved in design, implementation, analysis, interpretation, regulation, inspection, and publication of clinical trials ◆ Include users of results (e.g., health care providers, doctors, patients) ■ **Seek international adoption and harmonization** ◆ Facilitate global adoption of proposed changes