

CTTI RECOMMENDATIONS: QUALITY BY DESIGN

“Quality” in clinical trials is defined as the absence of errors that matter to decision making—that is, errors which have a meaningful impact on the safety of trial participants or credibility of the results (and thereby the care of future patients).

CTTI recommends that quality be built into the scientific and operational design and conduct of clinical trials (“quality by design”) as follows:

1. Create a culture that values and rewards critical thinking and open dialogue about quality, and that goes beyond sole reliance on tools and checklists.

Encourage proactive dialogue about what is critical to quality for a particular trial or development program and, when needed, the development of innovative methods for ensuring quality. Discourage overreliance on checklists and inflexible “one size fits all” approaches that undermine creation of specific strategies and actions intended to effectively and efficiently support quality in a given study. Verify that quality and performance measures are aligned with incentives driving a culture that rewards critical thinking. For example, rewarding study teams who minimize the time to first patient enrolled may serve as a disincentive to devoting time to identifying and preventing errors that matter through trial design.

2. Focus effort on activities that are essential to the credibility of the study outcomes.

Rigorously evaluate study design to verify that planned activities and data collection are essential. Streamline trial design wherever feasible. Similarly, deploy resources to identify and prevent or control errors that matter in the study; in other words, determine those study activities that are essential to ensure the safety of trial participants and the credibility of key study results. Consider whether nonessential activities may be eliminated from the study to simplify conduct, improve trial efficiency, and target resources to most critical areas.

3. Involve the broad range of stakeholders in protocol development and discussions around study quality.

Engaging all stakeholders with study development is an important feature of quality by design. The process of building quality into the study plan may be informed not only by the sponsor organization but also by participation of those directly involved in successful completion of the study such as clinical

investigators, study coordinators and other site staff, and patients. Clinical investigators and potential trial participants have valuable insights into the feasibility of enrolling patients who meet proposed eligibility criteria, whether scheduled study visits and procedures may be overly burdensome and lead to early dropouts, and the general relevance of study endpoints to the targeted patient population. When a study has novel features in elements considered critical to quality (e.g., defining patient populations, procedures, or endpoints), early engagement with regulators should also be considered.

4. Prospectively identify and periodically review the critical to quality factors.

The CTTI Quality by Design [Principles Document](#) and [Toolkit](#) can be used to identify those aspects in each study that are critical to generating reliable data and providing appropriate protections for research participants (“critical to quality factors”), and to develop strategies and actions to effectively and efficiently support quality in these critical areas. For example, in a cardiovascular major morbidity outcomes trial, strategies to ensure that the survival status of all trial participants is captured would be critical, but source verifying participants’ temperature readings obtained as a part of vital sign assessments at routine study visits is unlikely to be considered critical to the successful outcome of the study. In addition, because new or unanticipated issues may arise once the study has begun, it is important to periodically review critical to quality factors to determine whether adjustments to risk control mechanisms are needed.

-
- ▶ *These recommendations are based on results from CTTI’s [QbD Project](#).*
 - ▶ *CTTI’s [Executive Committee](#) approved the recommendations.*
 - ▶ *Released in June 2015*