

DCRI Streamlines Protocol Using Quality by Design Thinking

DCRI Implements CTTI's Quality by Design Principles

SUMMARY

An investigator at the [Duke Clinical Research Institute](#) (DCRI) was recently supported the design and delivery of the PROACT Xa trial, sponsored by Cryolife, Inc. PROACT Xa aims to determine if patients with an On-X mechanical aortic valve developed by Cryolife can be maintained safely and effectively on apixaban rather than warfarin. The investigator and his team successfully applied CTTI's [Quality by Design](#) (QbD) principles to the study by emphasizing them as a logical approach rather than a corporate paradigm.

GOAL(S)

The DCRI investigator worked with his project team to prospectively reduce the risk of protocol amendments and other clinical trial challenges by implementing QbD principles.

CHALLENGES

Colleagues within the DCRI were unfamiliar with QbD as an approach, and there was concern that formally introducing QbD would seem overly bureaucratic and thus not be embraced by the team.

SOLUTION(S)

CTTI's first recommendation for QbD is that it not be prescriptive. Rather, the approach involves creating a culture that values and rewards critical thinking and open dialogue about quality, and that goes beyond sole reliance on tools and checklists. With this in mind, rather than introduce QbD formally, the DCRI investigator presented QbD thinking as a simple application of logic. He advocated for the trial to be designed with two key principles in mind: 1) some aspects of the trial will be more important than others, and appropriate prioritization is necessary; and 2) stakeholder engagement is critical to optimal trial design. These tenets are foundational to QbD thinking, and by introducing them as a rational, common sense approach versus a new, formal process, the investigator was able to facilitate team buy-in.

TAKING ACTION

QbD emphasizes focusing limited resources on proactively addressing "errors that matter to decision making." The DCRI team applied the same thinking with an ABCD model (below) that they developed, categorizing each element of the study as either critical (A), important (B), nice to have (C), or worthless (D), and allocating resources and effort accordingly. For example, although critical factors are likely to only represent around 5 percent of the project, these factors should command around 50 percent of the study team's effort. Conversely, somewhere around 50 percent of activities can often be safely categorized as "nice to have" that shouldn't command more than a small fraction (perhaps 5 percent) of the team's effort and resources.

	% of project*	% of effort*
A - Critical	5	50
B - Important	45	45
C - Nice to have	50	5
D - Worthless	0	0

**Percentages are used as directional guidelines for the team; they are not intended to be literally or strictly applied.*

QbD thinking also maintains that the only way to achieve a true assessment of risks is to involve the broad range of stakeholders in protocol development and discussions around study quality. In this case, those stakeholders included:

- The DCRI internal project team
- Cryolife (the sponsor)
- U.S. Food & Drug Administration (FDA)
- Steering Committee of clinicians, surgeons, and investigators
- The Data and Safety Monitoring Board (DSMB)

Although the team for PROACT Xa did not include patients, the DCRI is working on ways to formally include these important stakeholders in future studies and recommends inclusion to researchers applying QbD. The team also did not initially engage with regulators from all countries in which the trial recruited, which proved challenging later on, as different regulatory agencies had different views on how to collect adverse event data. Engaging regulators from multiple countries will therefore be an important consideration for future QbD efforts.

The PROACT Xa team held project meetings once a week for an hour. In addition, they held meetings with subsets of the project team along with the sponsor once a week. Periodically in these meetings, the team engaged with FDA or the DSMB. The project leader and lead investigator of the study attended every call. The team identified three critical-to-quality (CTQ) factors (or, using the ABCD model, A-level critical factors) for PROACT Xa using multi-stakeholder engagement. Those were:

- *Rate of valve-related thromboembolic events across two groups* For this, the team discussed how to ascertain these events, which are the study's primary endpoint. They developed a telephone script to help coordinators talk with patients about symptoms and an algorithm for how patients should be evaluated if they have symptoms indicating potential endpoint events. The team determined that other adverse events could be collected as endpoints on the

case report form rather than as individual serious or non-serious adverse events.

- *Keeping patients on the study drug without crossover.* To mitigate this risk, the team established frequent contact with patients in both arms of the study and also used a central pharmacy to distribute drugs to patients, allowing the team visibility if patients were not getting refills.
- *Blinding appropriately.* The team determined that, although the study was open-label, the clinical events committee needed to be blinded. The team developed a plan to maintain blinding of people who do not need to know unblinded information.

IMPACT

By using QbD principles, the DCRI team thoughtfully and strategically designed the trial, most of which was executed remotely. Using QbD thinking, the investigator and his team brought together key stakeholders (including the sponsor, FDA, clinicians, surgeons, investigators, and the Data and Safety Monitoring Board) to align on what study factors are most important. They eliminated multiple facets of the study that were adding unnecessary complexity, while still answering the primary question the team set out to answer.

ADVICE

As other DCRI studies conclude, the team assesses how QbD thinking could have impacted the study as a whole to define any lessons applicable to subsequent efforts. Below are the four guiding principles used to assess the quality of the studies.

1. Have we enrolled the right participants according to the protocol with adequate consent?
2. Did participants receive the assigned treatment and did they stay on the treatment?
3. Was there complete ascertainment of the primary and key secondary efficacy and safety outcomes?
4. Were there any major (i.e., that impact participant safety or the integrity of the data) Good Clinical Practice (GCP) related issues?

The DCRI team has intentionally taken the approach of not trying to implement every part of QbD perfectly in this project or in every project. When teams have tried to be perfect in the past, they start viewing QbD as something separate from the trial – something new, an additional process. According to the PROACT Xa investigator, it does not need to be complex. Once teams start thinking with their QbD hat, they realize it is a natural approach to reasoning through a trial design.

ORGANIZATION

Duke University

CONTACT

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ORGANIZATION TYPE

Academia

IMPLEMENTATION DATE

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TOPIC

Quality

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