



Quality by Design (QbD) Case Study: Duke Clinical Research Institute

OVERVIEW

An investigator at the Duke Clinical Research Institute (DCRI) recently supported the design and conduct the PROACT Xa trial, sponsored by Cryolife, Inc. PROACT Xa aims to determine if patients with an On-X mechanical aortic valve can be maintained safely and effectively on apixaban rather than warfarin. The investigator wanted to try to streamline the trial, reduce the risk of protocol amendments, and avoid other challenges by implementing QbD principles.

Snapshot: PROACT Xa Trial

- ▶ Prospective, multicenter, randomized trial
- ▶ 1,000 participants (500 in each arm) who have the On-X aortic valve
- ▶ 60 North American sites
- ▶ Followed for 2 years minimum, average 3.5 years follow-up
- ▶ ClinicalTrials.gov Identifier (for additional study details): [NCT04142658](https://clinicaltrials.gov/ct2/show/study/NCT04142658)

CRITICAL TO QUALITY FACTORS (CTQs)		
Factor	Specific Consideration	Action(s) Taken
Procedures Supporting Study Endpoints and Data Integrity	Rate of valve-related thromboembolic events across the two groups The population and drugs being studied are well known and extensively studied	<ul style="list-style-type: none">▶ Discussed how to ascertain valve-related thromboembolic events, the study's primary endpoint▶ Created a telephone script for coordinators to discuss symptoms with patients and to ascertain potential events▶ Developed an algorithm for how symptomatic patients should be evaluated for potential endpoint events▶ 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
Withdrawal Criteria and Trial Participant Retention	Keeping patients on the study drug – no crossover	<ul style="list-style-type: none">▶ Established frequent contact with patients in both arms (this supports randomization, and also allows the team to reinforce study drug adherence)▶ Used a central pharmacy to distribute drugs to patients, allowing the team to know about medication adherence
Data Monitoring and Management	Blinding appropriately in an open-label trial	<ul style="list-style-type: none">▶ Determined that, although the study was open-label, the clinical events committee needed to be blinded▶ Developed a plan to maintain blinding of people who do not need to know unblinded information

CTQ Commentary

The team considered including bleeding risk in patients with mechanical valves as a CTQ factor, but these patients are typically lower-risk than other populations where apixaban has been demonstrated to be safer than warfarin, and the team had no reason to differentiate their bleeding risk from other populations. For these reasons, the team initially decided to not adjudicate bleeding. However, regulators and some investigators disagreed and felt bleeding was important to weighing risk versus benefit, so bleeding was moved to an “important” though not “critical” factor. The other activity the DCRI team considered as a CTQ factor was collection of serious and non-serious adverse event data. Given the safety profile of both drugs, and the team did not consider collecting more data on non-serious adverse events to be essential, and this was therefore rejected as a CTQ factor.

Results

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.

STRATEGIES IN DETAIL

Below are suggestions from this DCRI study team for effective implementation of QbD.

ABCD Approach to CTQ Assessment

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.*

Ensure Multi-Stakeholder Engagement

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.

Addressing barriers to engagement: Once a team brings together stakeholders, one of the barriers to meaningful engagement is that someone has to manage the diverse — and sometimes conflicting — perspectives. This DCRI team recommends:

- ▶ Thinking through — in advance — how information and decisions will flow in a clinical trial team, so that input is incorporated, but teams don't get bogged down in deliberation.
- ▶ Having an operational lead that partners with, and makes decisions together with, the principal investigator.
- ▶ Mentoring and involving a younger principal investigator so that senior investigators can focus on the critical tasks (As) and don't have to comment on the less meaningful elements ranked B, C, or D.

Meetings: Have more than one meeting across stakeholders. The PROACT Xa team held project meetings once a week for an hour each. 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 regulators or the DSMB. The operational lead and lead investigator of the study attended every call.

Present QbD as Logical Thinking

With most of the study team unfamiliar with QbD, the DCRI investigator was concerned that formally introducing QbD and associated technical language would seem overly bureaucratic and thus not be embraced by the team. For that reason, the investigator's approach was to present QbD thinking as logic, rather than a formal or different paradigm.

Measure Success

As other DCRI studies conclude, the team now 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 conducted.

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?

Build QbD Implementation to Meet your Needs

Don't try to implement every part of QbD perfectly into every project. When DCRI teams have tried to be perfect in the past, they started viewing QbD as something separate from the trial — something new, an additional process. According to this DCRI team, 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.