

## Quality by Design (QbD) Case Study: Alexion

### OVERVIEW

Alexion was set to launch a phase 3 trial to register and file its second product. It was a pivotal make-or-break moment for the company, so getting the process right was absolutely critical. The team applied Quality by Design (QbD) principles in the protocol development process, uniting cross-functional stakeholders early in the process to build a streamlined, simple protocol. This resulted in a successfully launched trial that cleared regulatory approval on time and brought the product to market.

#### Snapshot: Pivotal Rare Disease Trial

- ▶ Open-label, phase 3 trial in an ultra-rare disease population
- ▶ Largest trial ever run in that population with 246 patients globally, 126 sites, and 25 countries
- ▶ Patients randomized 1:1 to receive study drug vs. active comparator
- ▶ Goal to demonstrate non-inferiority
- ▶ ClinicalTrials.gov Identifier (for additional study details): [NCT02946463](https://clinicaltrials.gov/ct2/show/study/NCT02946463)

CRITICAL TO QUALITY FACTORS (CTQs)		
Factor	Specific Consideration	Action(s) Taken
Procedures Supporting Study Endpoints and Data Integrity	Ensuring enrolled patients have the opportunity to meet the primary endpoint before starting study drug	Transfusion avoidance was a primary endpoint, and it would have confounded the interpretation of the study data if enrolled patients needed a transfusion even before starting the study drug. Thus, the study was designed such that patients had hemoglobin levels checked within five days prior to randomization, and that any immediately-necessary transfusions were administered prior to randomization and before starting the study drug.
Procedures Supporting Study Endpoints and Data Integrity	Compliance with drug therapies	The threshold was set to minimize missed doses of the study drug and comparator. This was because the team knew that missed doses of a complement inhibitor could cause the disease to come back rapidly, confounding analysis.
Randomization	Correctly stratifying patients within six stratification buckets based on two different factors that would affect patients' response to therapy	The study's medical monitor conducted the stratification. The study investigator submitted appropriate case report form pages before the patient could be randomized.
Withdrawal Criteria and Trial Participant Retention	Prevention of patients dropping out	Implemented a high degree of patient follow-up to prevent attrition bias.

## CTQ Commentary

Halfway through the study, the team noticed a problem with “tabletop hemolysis.” (This occurs when, either due to mishandling or letting a sample sit on the tabletop too long, the blood cells in a blood sample release an enzyme, making it look like patient is having a lot of hemolysis.) After discussion of whether to make this one of the CTQ factors, the team ultimately decided not to. Because they were already monitoring each case that had happened, the team reasoned that they had a very clear protocol that they put into effect at sites where tabletop hemolysis occurred. Therefore, the team decided this was already controlled enough and did not merit CTQ status.

## Results

The trial met its timeline, and when the U.S. Food and Drug Administration approved the investigational product, the news was met with celebration across the organization. In an all-hands meeting with the Alexion’s CEO, every single product team member mentioned quality as a critical driver to the trial’s success. An organization that once saw quality as a tick box to be checked was transforming into one with a holistic quality perspective and individual ownership across the enterprise. This change, Alexion’s leaders say, is the true value of implementing QbD. The study had zero protocol amendments related to CTQ factors, and the intense focus on these factors meant that none of them ever reached the thresholds the team deemed problematic.

## STRATEGIES IN DETAIL

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

### Lean on QbD Experts

A new member of Alexion’s leadership team had experience applying QbD, so she was selected to partner with the organization’s vice president of Medical Development to pilot a QbD process for the pivotal phase 3 trial.

### Think Through Challenges

Although Alexion was becoming a mature company, systems and processes were still limited, and experience with phase 3 trials among the team was minimal. In addition, the trial’s timeline was very short. And, as with many sponsors at the time, discussions around “quality” tended to be from an audit perspective rather than a proactive focus on risks.

### Leverage Existing Tools

The co-chairs used material from CTTI’s [QbD Toolkit](#) to help the team understand QbD principles and how the approach can optimize a trial’s chance of success. Next, the team applied the QbD methodology to the trial, using the [Principles Document](#) to help identify CTQ factors. After identifying four CTQ factors, they developed a risk mitigation plan that connected directly back to those factors.

In alignment with CTTI's recommendations, Alexion also established a steering committee to hold the team accountable for keeping quality at the forefront of discussions during study planning and ensuring team alignment. The team's development of a product QbD steering committee not only served to guide the product's QbD journey, but also helped the team apply the QbD processes to a parallel indication for a compound that later emerged.

### **Ensure Multi-Stakeholder Engagement**

The study team collaborated with operational colleagues, medical team members, investigators, and its CRO to get a sense of potential difficulties in executing the study protocol. For instance, one primary endpoint around transfusion avoidance had very specific transfusion criteria to which investigators had to adhere. Medical team members gave valuable feedback in their perception that this criteria would be complex and difficult for an investigator to comply with properly. That input drove the decision to check patients' hemoglobin levels prior to randomization, and avoided a situation where study participants could fail the primary endpoint before starting the study drug.

The multi-stakeholder team had a meeting every month, during which they presented slides with CTQ factors and then diligently tracked them..

- ▶ For these meetings, clinical trial leads assembled the data, and worked closely with the Quality function. The study team kept track of associated metrics, and whenever they saw a potentially challenging event, they collaborated on how to prevent further events from occurring.
- ▶ Because of the trial's pivotal nature and strict thresholds for missed doses, the team monitored the study aggressively, including having medical monitors visit multiple sites, and many visits to high-enrolling sites.

### **Don't Use QbD as a Gatekeeping Strategy**

From this team's perspective, there is nothing about QbD that needs to slow down the timelines. It should not be a rate-limiting step. For example, if a team does not fully identify CTQ factors at the protocol concept sheet stage as CTTI recommends, it is not too late. The team should still identify them with as much rigor and thought as possible, even if it is later than ideal. QbD is meant to help teams, not hinder them.

### **Keep Evolving the Approach**

Alexion has since evolved its QbD processes to better serve its needs. For example, product-specific QbD steering committees were disbanded in favor of portfolio-wide risk-based quality management steering committees that ensure the quality approach is calibrated across all products. These teams include development heads for therapeutic areas, as well as leaders from regulatory, clinical operations, quality, and data management. Each drug program in the company also has a quality steering committee, which includes the product team lead, quality operations leads, and more. In a recent Good Clinical Practice inspection, the organization's approach to quality was commended as one of the most mature and thoughtful the inspector had seen.