

Quality by Design (QbD) Case Study: University of Oxford CTSU

OVERVIEW

University of Oxford's Clinical Trial Service Unit & Epidemiological Studies Unit (CTSU), - which aims to generate reliable evidence from observational epidemiology and randomized trials that lead to practical methods of avoiding premature death and disability, has long been implementing an approach to clinical trial design and conduct that aligns with QbD.

This case study captures CTSU's implementation of QbD thinking in the ASCEND (A Study of Cardiovascular Events in Diabetes) trial, which was conducted to determine whether aspirin and/or omega-3 fatty acids (fish oils) reduced the risk of heart attacks and strokes in people with diabetes who did not already have any existing problems with their heart or blood circulation when they started the study.

Snapshot: University of Oxford CTSU – the ASCEND Trial

- ▶ 15,500 UK participants with diabetes
- ▶ 2x2 randomized factorial design (aspirin vs. placebo and, separately, fish-oil supplements vs. placebo)
- ▶ Streamlined mail-based approach in which participants were identified via local and central diabetes registers and invited by mail to participate, with follow-up conducted by mail
- ▶ 7.5 years average follow-up
- ▶ ClinicalTrials.gov Identifier (for additional study details): [NCT00135226](https://clinicaltrials.gov/ct2/show/study/NCT00135226)

CRITICAL TO QUALITY FACTORS (CTQs)		
Factor	Specific Consideration	Action(s) Taken
Recruitment	Ensuring sufficient statistical power/sample size	<ul style="list-style-type: none">▶ Ensured multidisciplinary collaboration▶ Widened primary endpoint to include transient ischemic attacks▶ Increased sample size from 10K to 15K
Adherence	Making sure patients continued taking the treatment	<ul style="list-style-type: none">▶ Ensured multidisciplinary collaboration▶ Conducted surveillance
Retention	Keeping patients engaged in a long study (initially 5 years, but extended to 7.5)	<ul style="list-style-type: none">▶ Conducted surveillance▶ Established Electronic Health Record (EHR) plan to supplement information if needed

CTQ Commentary

In order to keep costs down, the study team designed a mail-based approach to recruitment and follow-up. With the necessary approvals in place, UK researchers can gain access to electronic health records, which can be used to identify potentially eligible patients for invitation to trials. Ensuring standard, clinic-based recruitment was therefore not considered as a potential CTQ, as centrally held diabetes registers offered a sufficient recruitment alternative. However, it was vital that the team monitored the rate of accrual of primary endpoints to ensure adequate statistical power in the trial. In this low-moderate risk, primary prevention population, the blinded annual rate of serious vascular events was found to be lower than expected, so the study population size and duration of follow-up were both increased to maintain statistical power.

Given the nature of the study treatments and well-established safety profile, in-person doctor visits at clinics or sites were not considered critical, and patient-reported outcomes could replace in-person visits to clinics. If participants failed to return study questionnaires, information could be gained via primary care physicians and supplemented by access to electronic health records.

The design of ASCEND included optional baseline blood and urine sample collection during the pre-randomization run-in phase. Blood and urine samples were not considered CTQ as they were not required to answer the key questions being addressed in ASCEND. However, the collection of optional samples (achieved in $\frac{3}{4}$ of the participants) allowed further characterization of the study population. This exercise was funded by a separate project grant from the British Heart Foundation, so would also not impact budget.

Results

Using QbD principles, the CTSU team successfully streamlined the ASCEND trial design, which allowed it to be completed on budget. Information on approximately 600,000 people listed on 58 centrally held diabetes registers was obtained, and 300,188 potentially eligible patients were invited to join the study. In addition, 785 provider practices mailed invitations to 120,875 patients. A further 2,340 potential study participants were identified via other routes. In the end, 26,462 patients entered the two-month, pre-randomization, run-in phase, and 15,480 were randomized.

STRATEGIES IN DETAIL

Below are strategies the CTSU study team leveraged for effective implementation of QbD.

A Rich History of Large Simple Trials with Streamlined Design

In 1988, the University of Oxford successfully streamlined the ISIS-2 trial of 16,000 patients by building the protocol with a proactive focus on errors that matter to decision-making, patient safety, or interpretation of results—what would later be known as QbD thinking. The entire final ISIS-2 protocol was 16 pages, including a double-page spread poster for emergency rooms that summarized everything needed to recruit participants.

From the success of this trial, Oxford's trial design philosophy was built. When ASCEND launched in 2005, the CTSU team was able to build on lessons learned and once again achieve a streamlined protocol aligned with the principles of QbD.

Multidisciplinary Approach to CTQ Factor Assessment

CTSU suggests that, in planning a clinical trial, researchers should bring the right stakeholders to the table. Establish arranged team meetings, but also embed the multidisciplinary approach into day-to-day working.

- ▶ Key individuals for ASCEND who met on a regular and ad-hoc basis included the principal investigators, clinical trial manager, lead computer scientist programmer who oversaw the development of all the key programs, drug supply lead, and statistician.
- ▶ ASCEND also included peripheral stakeholders, such as people who sat on a trial steering committee, other trialists, a primary care physician, and a lay member giving the patient perspective. These individuals met once or twice a year.

A 'Clean Slate' Approach to Trial Design

When designing a trial, many organizations tend to simply copy and modify the protocol of the most recent similar trial. CTSU suggests a different approach. Start each protocol from scratch, and ask, "What is the scientific question you are trying to answer?" Determine that, and build out only the essential elements needed in the protocol to answer that question reliably.

An EHR Backup Plan to Mitigate Important Risk

One of ASCEND's identified CTQ factors was keeping patients engaged and adherent to the study. In response, the team established a hierarchical, timeline-based loss-to-follow-up strategy.

- ▶ If the team received no response from participants to their mailed questionnaires (including reminder mailings and attempts to contact by phone), they reached out to the patient's primary care doctor for assistance.
- ▶ If the primary care doctor could not provide the questionnaire responses, the ASCEND team turned to electronic health records to fill in gaps in follow-up information.

A System for Tracking CTQ-Related Metrics

CTSU closely monitored all metrics with the potential to impact CTQ factors by means of regular review of relevant reports from the study database.

- ▶ Tracked data points included how many ASCEND questionnaires were returned, time and date of return, number of questionnaires fully completed, and proportion of patients still taking the study treatment.
- ▶ Each element was mapped in a single sheet to quickly identify and react to any problem areas.
- ▶ Each management meeting specifically included a review of each CTQ factor and the data to support its progress.

Strong Investigator Relationships that Reinforce QbD Thinking

Organizationally, CTSU embeds the tenets of QbD thinking across its work via close collaboration and ongoing investigator training. Particularly in the UK, where the University of Oxford runs multiple large trials for cardiovascular disease, it has established a strong network of repeat investigators who understand the organization's commitment to the principles of QbD trial design. To reaffirm its philosophy, CTSU requires investigators train not only on the protocol, but also on understanding why QbD thinking is an important component of the work.

Commitment to Keep the Focus

In applying QbD principles, it is helpful to go back to the study question continually. What are you trying to determine? Is each component of the trial design necessary to answer the question? Continuing to keep the study question front of mind will help eliminate unnecessary components that do not directly address the trial's aim. QbD is, at its heart, about focusing energy on those trial components that matter to quality and not getting distracted by those that do not.