

## Quality by Design (QbD) Case Study: The Medicines Company

### OVERVIEW

The Medicines Company (acquired by Novartis in January 2020) was a small pharma company that often conducted large global trials. This case study describes The Medicine Company's application of QbD to the protocol development of the ORION-4 study. ORION-4 is co-sponsored by the University of Oxford, with a central coordinating office based at the University's Clinical Trial Service Unit (CTSU). The trial aims to find out if a new cholesterol-lowering injection safely reduces the risk of heart attacks and strokes in people who have already had one of these conditions, or who have had an operation or procedure to unblock their arteries.

#### Snapshot: ORION-4 Trial

- ▶ Double-blind randomized trial
- ▶ Study population to include 15,000 people aged 55 years or older, with established cardiovascular disease
- ▶ Half receive inclisiran injections, and half receive inactive placebo
- ▶ Participants are asked to stay in the study for about 5 years
- ▶ Trial is a collaboration between three distinct organizations (co-sponsors: The University of Oxford and The Medicines Company (subsequently Novartis), in collaboration with researchers at the TIMI Study Group at Brigham and Women's Hospital in Boston)
- ▶ Limited funding
- ▶ ClinicalTrials.gov Identifier (for additional study details): [NCT03705234](https://clinicaltrials.gov/ct2/show/study/NCT03705234)

CRITICAL TO QUALITY FACTORS (CTQs)		
Factor	Specific Consideration	Action(s) Taken
<b>Recruitment</b>	Recruitment of the right patients (population required was known to be difficult to recruit)	<ul style="list-style-type: none"> <li>▶ In order to be activated, sites were required to create a list of patients they could invite to participate as soon as the study was started</li> <li>▶ Since part of the study was in the UK, the team could use hospital discharge information, provided via a central portal (NHS Digital), to identify patients. Rather than going to each hospital for individual downloads, the National Health System's central system allows access to identify and contact people in one location to facilitate study start-up</li> </ul>
<b>Retention</b>	Patient drop-out or noncompliance with the intervention	<ul style="list-style-type: none"> <li>▶ In the study's IT system, the team developed modules that allowed sites or regional coordinating centers to have a real-time view of late appointments, missed appointments, or people who didn't receive dose of study medication</li> </ul>

		<ul style="list-style-type: none"> <li>▶ The team established a communications module within the IT system to chat with study coordinators, enabling real-time troubleshooting for issues during trial</li> <li>▶ The team purposely established a long, two-month run-in period, between the first trial visit and the start of the randomized treatment. Although it may seem counterintuitive, the rationale was that if they were still interested in participating two months later, they would likely stay for the 5-year duration of the trial</li> <li>▶ Sites with good track record in patient retention were selected for the trial</li> </ul>
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## CTQ Commentary

Safety data collection is an important element for this trial. Given the trial design and the stage of the drug development, it was appropriate not to collect non-serious adverse events (AEs) in this trial. This approach streamlined and simplified data collection for the trial, however necessitated process redesign at The Medicines Company, where processes were typically configured for collection of all AEs. An important part of the process redesign was making sure that the whole team was aligned and comfortable with the approach.

The CTQ process helped the team maintain a streamlined focus on the goal of the trial. The objective of the trial is to measure effect on clinical outcomes. Therefore, it was not necessary to measure effect on cholesterol levels, even though this is the primary effect of the drug. The team found it is important to be relentless in questioning, for every study procedure: Is this helping to answer the trial question? If no, throw it out. If yes, let's figure out how to do it in the most efficient way. By challenging each other's assumptions and usual ways of working, the team was able to create a streamlined trial design.

This trial is using a direct data capture tool developed by the University of Oxford. A word of advice for trials utilizing direct data capture: Ensure the protocol is designed so that it does not depend on information patients are unlikely to remember. If the trial is aligned with that approach, quality is better. Otherwise, teams may be left chasing pieces of paper for the information.

## Results

ORION-4 is currently still recruiting, but the team has seen a faster-than-expected rate of recruitment with the implementation of QbD to the protocol design and execution. Although QbD was already the standard practice for protocol development and execution for both The Medicines Company (subsequently Novartis) and Oxford CTSU, the two sponsoring organizations learned from each other's approaches to implementation of QbD principles.

## STRATEGIES IN DETAIL

Below are suggestions for effective implementation of QbD.

### Assess Your Challenges

Global trials with large populations tend to bring complexity from both a scientific and operational perspective. The team needed to develop a nimble quality strategy that it could scale up while also ensuring the approach was risk-based, allowing the small team to maintain focus on the trial's critical components.

### Ensure Multi-Stakeholder Engagement

Protocol development for ORION-4 was a collaborative effort between the academic groups at CTSU and the TIMI Study Group, and The Medicines Company. It involved the whole clinical team, including individuals responsible for design (medical, scientific, or regulatory) as well as data management, safety, drug supply, operations, site managers, etc. The team designing the trial was also the team running the trial, which avoided the need for handoffs.

- Make sure the team understands why each component is important in order to design the trial in the context of quality, as well as what components are critical in the protocol versus what is optional, and what is included because of regulatory requirements. Alignment is key.

### Consider Four Core QbD Questions

Regardless of whether the protocol being designed is for a small phase 1 or a large global trial, four core questions never change:

1. Why do we need this component (or do we)?
2. Can we do this in an easier way?
3. What are the drivers of this component?
4. Can we get this information elsewhere?

Continually returning to these questions during multi-stakeholder collaboration will help keep the protocol as streamlined and focused as possible.

### Allow for Flexibility

It is critical that a specific QbD strategy is developed for each trial, reflecting its unique challenges—be it in design, operation, team structure and organization, resources, etc.

Resisting the urge to heavily formalize the process across an organization can help QbD embed itself as a common sense, helpful approach rather than a bureaucratic to-do that unnecessarily burdens teams.