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Quality by Design in Clinical Research

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Joseph M. Juran introduced the term "Quality by Design (QbD)" in his book, "The Quality Trilogy: A Universal Approach to Managing for Quality." The basic idea of QbD is to build quality into a product during the design process, rather than to find and remove defects during the production process. Unlike Six Sigma, a data-driven method of continuous improvement, it does not rely on statistical analysis. However, QbD can rely on Six Sigma to ensure high quality.

The FDA's QbD initiative originated in the Office of Biotechnology Products (OBP). In 2007, the FDA partnered with Duke University to establish the Clinical Trials Transformation Initiative (CTTI), which promotes the use of QbD for the discovery, development and manufacture of drugs. CTTI's Quality by Design project explicitly links QbD with monitoring (a quality control (QC) process) to focus "resources on the errors that matter to decision making during a trial, such as primary endpoints and patient safety."

In 2009, the International Conference on Harmonisation (ICH) incorporated QbD in its Q8(R1) Pharmaceutical Development guideline (corrected in Q8(R2)). This guideline defines QbD as "a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management."

Clinical research, which spends about as much on site monitoring and data cleaning as it does on the conduct of clinical studies at investigative sites, illustrates the pitfalls of relying on inspections and rework to deliver quality. Risk-based monitoring (RBM) is a way to make the inspection process (and quality feedback loop) more efficient and effective.

The QbD model consists of six steps:

1. Establish the product design targets and goals.
2. Define the market and customers that will be targeted.
3. Discover the market, customers and societal needs.
4. Develop the features of the new design that will meet the needs.
5. Develop or redevelop the processes to produce the features.
6. Develop process controls to be able to transfer the new designs to operations.

Note that the process controls that ensure high quality, e.g., RBM, are part of the model.

A site that uses a quality management system (QMS) to avoid making errors in the first place is employing the QbD concept. A QMS provides the structure for consistent, high-quality performance that meets internal, customer and regulatory requirements with five elements:

- A system for hiring, onboarding and developing competent and motivated personnel
- Standard operating policies and procedures (SOPs) and work instructions, which, if followed, will deliver high-quality outcomes
- A training program so that personnel know how to follow the SOPs
- A quality control program to ensure that the SOPs are followed

- Metrics to measure performance against the SOPs, detect issues to be addressed, and drive improvement

Note that the first three elements are intended to prevent errors (QbD), while the last two are designed to find, correct and also prevent errors. In the QbD model, a site's QMS is an integral part of the service it offers to study sponsors.

"Idiot proofing," i.e., creating processes that are error-proof, is a form of QbD. For example, a protocol might require that subject weight be recorded to the nearest pound. However, a scale might measure weight to the nearest tenth of a pound. The study coordinator might make a rounding error, but if the EDC accepts weight to the nearest tenth of a pound and then rounds it to the nearest pound itself, the error can be eliminated.

Juran defines "quality" as (a) the presence of features that create customer satisfaction and (b) the reliability of those features, i.e., the absence of "dissatisfactions." In other words, a high-quality product reliably delivers the features that customers want. In a low-quality product, the features that customers want are absent or unreliable. Of course, different customers want different packages of features, and some features conflict with other features. For example, a customer might want a product with lots of bells and whistles, but also a product that is very easy to use — a tough combination to deliver.

Study sponsors, in their rush to complete clinical development, often do not follow the QbD process. As a result, they try to conduct studies with the wrong endpoint for patients, the wrong sites (e.g., neurologists vs. internists), impractical eligibility criteria, infeasible visit schedules, etc.

In clinical research, protocols have been growing more complex, with extra tests, procedures and data points not needed for the primary and most important secondary endpoints. Complexity makes protocols inherently more error prone, the opposite of QbD.

If a sponsor were to apply QbD principles to site selection, it would work only with sites that reliably hit their enrollment targets and deliver high-quality data, even if the site cost per patient is very high. With RBM, the cost of monitoring these sites would be low. Instead, sponsors often employ numerous unreliable sites that require intensive monitoring, so the sponsor ends up with low quality data, a longer timeline, and an even higher cost per patient.

If a site were to apply QbD principles, it would invest in training, technology and other infrastructure and processes to ensure reliably high enrollment and data quality. While many leading sites find these investments worthwhile, it requires a leap of faith to make these investments today on the assumption that they will pay off tomorrow in higher volume, higher prices, and lower rework costs.

Conclusion

Quality by Design is not rocket science. It incorporates sensible principles that are hard to disagree with. The challenge for the clinical research enterprise is to invest the time to apply these principles up front to build quality into the study process. It's one of those "pay me now or pay me later" situations where "pay me now" is clearly the right choice.

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