The COA Qualification Process: Where Are We Now and What Have We Learned?

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With the release of the final U.S. Food and Drug Administration (FDA) guidance for the qualification process in January 2014 titled *Qualification Process for Drug Development Tools,*[1] a number of qualification projects are actively underway for a wide variety of conditions, including ulcerative colitis, Crohn's disease, asthma, cystic fibrosis, functional dyspepsia, gastroparesis, and non-small cell lung cancer, to name just a few. Currently, there are 86 Drug Development Tool (DDT) projects in various stages within the qualification program, of which 55 are Clinical Outcome Assessments (COAs).[2]

The qualification process is intended to expedite the growth of publicly available DDTs for a specific context of use in clinical trials to expedite drug development and regulatory review. It is designed to encourage scientific collaboration from multiple sponsors to increase efficiencies and reduce the cost burden associated with developing a COA. To date, however, only one COA, The EXAcerbations of Chronic pulmonary disease Tool (EXACT), submitted by Evidera, has been issued qualification.[3]

Evidera is currently involved in a number of qualification projects across various therapeutic areas, including gastroenterology (ulcerative colitis, Crohn's disease, and gastroparesis), infectious diseases, pulmonary/respiratory diseases, and pharmacology/toxicology. Given all this recent activity, it is time to reflect on the current qualification process and address some of the advantages and challenges that the pharmaceutical industry faces with this process, specific to COA development, and examine how these challenges might be mitigated to maximize future qualification work for instrument development.

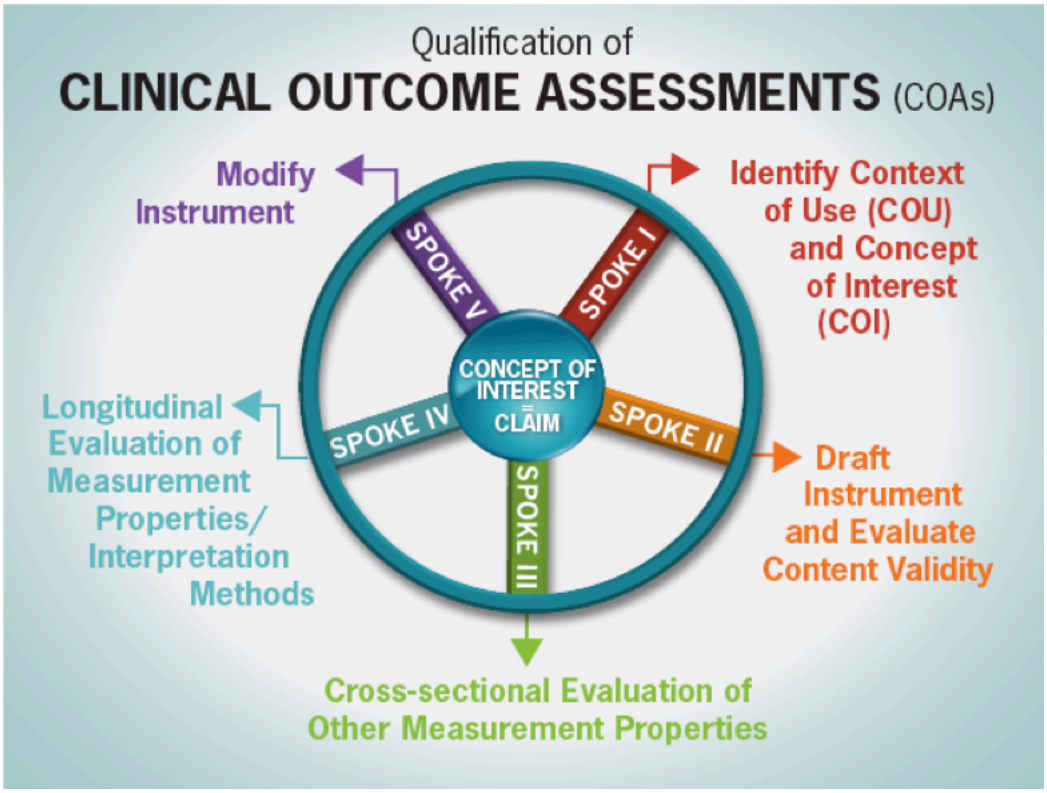
The qualification process

Since the release of the guidance in 2014, the process has been slightly modified to increase efficiency and obtain earlier qualification. The COA wheel and spokes diagram (Table 1) depicts the key components of instrument development and the points at which qualification may occur.[2]

Spoke I corresponds to the initial stage of the process, whereby a letter of intent is submitted, addressing the concept of interest that the instrument seeks to measure (e.g., specific symptom presence or severity, limitations in daily activities); its proposed clinical context of use for which qualification is being sought (target population, study design, endpoint positioning); and rationale for use in drug development (addressing an important unmet need).

Spoke II encompasses the qualitative phase of instrument development up through the evaluation of content validity, while Spoke III includes cross-sectional evaluations to examine the structure (domains) of the measure, develop a scoring system, and evaluate psychometric properties of reliability and construct validity. At this point in the process, the consortium can elect to submit the available evidence for COA qualification. Qualification at this time will enable the COA to be used as an exploratory endpoint in clinical trials, for the purpose of collecting longitudinal data to assess ability to detect change, identify responder definition(s), and provide guidelines for interpretation of treatment benefit (Spoke IV). Once all measurement properties have been adequately examined, all evidence will be reviewed to support COA qualification for use as primary or secondary endpoints of effectiveness.

Table 1. COA qualification spokes and wheel diagram



Advantages of the qualification process

Based on Evidera's experience with qualification projects, which includes working with as few as two sponsors for COA development as well as with larger working groups such as the COPD Foundation,[4] several key advantages of the qualification process were identified related to increased scientific robustness of instrument development, ongoing engagement with the FDA, and the potential for reduced costs to individual sponsors for their overall drug development programs.

Scientific robustness

The collaboration of multiple industry leaders lends itself to the increased scientific robustness of studies conducted to support the COA qualification. Generally, consortiums are set up to include industry sponsors who work in collaboration with a steering committee, represented by individuals who have clinical knowledge as well as those with expertise in instrument development and measurement. With pooled resources, both intellectual and monetary, the collaborative interaction and sharing of ideas has the added advantage of advancing the science of the therapeutic area itself.

FDA engagement

The FDA's Center for Drug Evaluation and Research (CDER) emphasizes that early and continued interactions with the FDA during the instrument development process are not only encouraged, but seen as critical to the success of the program.[2] The COA Qualification Review Team (QRT) is comprised of representatives from three groups: The Study Endpoints Team (from The Study Endpoints and Labeling Development [SEALD] staff), the appropriate review division(s), and the Office of Biostatistics.

While formal decisions at key points in the qualification process are provided in written format by the QRT, working groups generally have relatively easy access to the QRT, typically via teleconferences. These informal meetings are meant to be collaborative in nature and may provide sponsors with key insights into the "thinking" of the FDA as well as provide an opportunity to get clarification and discuss any outstanding issues at key junctures in the COA development program to keep the process moving forward in an efficient manner.

Cost

It is generally assumed that collaboration with multiple sponsors will reduce the overall costs related to the development of COAs for individual sponsors compared to costs associated with developing product-specific COAs within the context of individual drug development programs. However, the potential to reduce costs is often contingent on the number of sponsors involved in the consortia and the complexity of the overall project.

It is also important to keep in mind that obtaining COA qualification generally takes a number of years, with obvious implications for cost. While the cost related to qualification work can seem rather high to individual sponsors, it is important to note that overall the costs may be less (or equal) to costs associated with individual drug programs, especially when one considers the possibility that a drug-specific COA may not be accepted by the FDA as a primary or secondary endpoint after resources have been expended for its development.

Disadvantages of the qualification process

FDA review timeline

There isn't one. The QRT is not obligated, nor held accountable, to review qualification submissions on a specified timetable. The QRT is essentially a volunteer group with the legal obligation and priority for review centered on the traditional investigational new drug/new drug application (IND/NDA) approval process for drug development as set forth by the 1992 Prescription Drug User Fee Act (PDUFA). That said, CDER continues to encourage instrument development and qualification. While qualification reviews submitted by Evidera were essentially put on hold during 2014 due in large part to a backlog of PDUFA obligations and limited staff at SEALD, recent communications with the QRT indicate that it is fully staffed and committed to timely review.

Consensus

Achieving consensus among multiple industry sponsors can be challenging. At the outset, CDER requests a well-defined COA concept (i.e., proposed instrument) and specific context of use to ensure that, once qualified, the instrument is fit for purpose to measure a primary or secondary endpoint in a specific clinical context of use. While the context of use may be modified or expanded over time as additional data are collected, the initial context of use (and other key components) is critical to CDER's decision to accept the DDT request and advance to the consultation and advice phase of qualification. Given the extended timelines associated with the qualification process, there also is likely to be a change in sponsor representation, causing the working group to revisit issues that were previously agreed upon.

Competing timelines and priorities

A number of qualification projects operate within a precompetitive framework (i.e., independent of specific drug issues), including PRO Consortia projects within the Critical Path Institute (C-PATH).[5] However, a number of smaller consortia groups have been formed to develop COAs within the context of the qualification process for use in drug development programs. Industry sponsor members who have come together independently to form a consortium and participate in the qualification program generally have different drug development timeline priorities that may impact decisions and collaboration.

Given the lengthy timeline associated with qualification, attrition may occur, whereby industry members may elect to leave the consortium before qualification, due to any number of changes within the respective companies (e.g., change in drug development priorities, failed molecule, change in company staffing, etc.).

Administrative logistics

The administrative logistics cannot be overstated. The legal process for contracting between industry sponsor members can take up to a year — delaying project commencement. Internal processes of each sponsor member must also be taken into account to allow for appropriate review of all essential documents within each organization. In addition, time must be allowed for the regulatory staff review required within each company.

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Mitigating challenges and moving forward

While the qualification process has the potential to increase efficiencies and reduce costs related to the COA development, there is little doubt that consortiums have faced a number of challenges during the past few years. It is unlikely that the administrative logistic challenges will change in the short term, although legal issues and contracting may become less cumbersome in the future as pharmaceutical legal departments become more familiar with consortium collaboration. There are, however, several ways to mitigate some of the other identified challenges to improve the current qualification process.

Managing expectations

It is important to manage the expectations of industry sponsors when forming a consortium. First and foremost, members should be aware that the process for developing COAs for qualification is "a marathon and not a sprint," with timelines that could span several years or more. With that in mind, sponsors are encouraged to pursue the traditional drug development approval path in parallel to the consortium activities. In addition, guidelines for consensus building need to be addressed, so that issues agreed upon are not revisited. Sponsors also need to keep in mind that all qualified COAs will be made publicly available (albeit through licensing agreements) for others (i.e., competitors) to use in their own drug development programs. Industry sponsors need to strategically assess their own needs and timelines, as they progress through the qualification process.

Sponsors with similar goals

Especially for smaller consortia groups, it is important to include industry members with similar objectives for COA development and similar timelines. The qualification process will proceed much faster and more smoothly if sponsors are able to develop a focused context of use for which the proposed COA would be used. As stated above, the context of use can always be updated and modified with additional data collection and re-submitted to the QRT at a later date.

Scientific dissemination

Have a plan for scientific dissemination to demonstrate short-term accomplishments. The qualification process for COAs can take years from inception to the issuance of qualification. Presenting posters and submitting manuscripts not only demonstrate to internal stakeholders that instrument development is progressing, but it can be beneficial in obtaining important "buy-in" from others in the industry or increasing interest among additional sponsors to join the consortium.

Summary

CDER continues to encourage instrument development and qualification, especially in areas with unmet needs. The qualification process is fairly new and continues to evolve as more and more industry sponsors, academics and patient advocacy groups get involved. While there are certainly challenges, most of these can be mitigated as lessons are learned to improve the overall process.

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