ENGELBERG CENTER for Health Care Reform at BROOKINGS

Enhancing the Development and Use of Patient-Reported Outcomes in Drug Development

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Meeting Summary

Capturing patient-reported outcome (PRO) measures is the most direct approach to gaining insights from patients about their symptoms, functional status, treatment preferences, and health-related quality of life. Over the last few years, there has been increasing interest among drug developers, clinicians, payers, regulators, and patients in the development and application of PRO instruments in the drug development process, particularly to support product labeling claims. Product labeling provides a formal summary of a drug's benefits and risks as approved by the U.S. Food and Drug Administration (FDA), and is a key source of information for patients and providers. The FDA released final guidance to industry on the use of PRO instruments to support labeling claims in 2009, and in 2014 released guidance formalizing a process to qualify instruments for use across multiple drug development programs. However, progress has been slow, owing to a variety of methodological, logistical, and communication challenges. Addressing those challenges will require the ongoing support and collaboration of all pertinent stakeholders, including drug developers, researchers, patients, PRO instrument developers, and regulatory agencies.

PROs in Drug Development and Labeling Claims

PRO measures include any report on the status of a patient's health condition that comes directly from the patient, without interpretation by another party.[1] In clinical research, PRO instruments are used to capture a range of concepts that are important to patients, including symptom burden, level of functioning, health-related quality of life (HRQoL), satisfaction with treatment, and treatment adherence. PRO instruments are also used in the drug development process to assess treatment risks and benefits, most commonly for drugs intended to alleviate the symptoms of chronic or disabling conditions. Particularly in the case of symptomatic conditions like migraine or irritable bowel syndrome, PRO instruments can serve as primary endpoints in clinical trials. They may also be used as secondary endpoints, which support the primary endpoints in a trial while providing a more comprehensive picture of treatment effect.

While the use of PROs in clinical trials has grown in recent years, this growth has been concentrated in particular disease areas, and some have argued that they are underutilized in several areas that would benefit from an increased focus on how patients feel or function in relation to their disease.[2,3,4] Of particular concern is the relative lack of PROs being used to support labeling claims. A recent review found that the number of PRO claims approved by the FDA for inclusion in drug labeling has declined in recent years, falling from 30% of drug approvals granted between 1997 and 2002 to 24% of drugs approved between 2006 and 2010.[5] Labeling claims are important to manufacturers seeking to distinguish their products in the market, as well as to clinicians and patients seeking information on a drug's effects. Sponsors routinely use PRO instruments to collect a range of HRQoL data in pivotal clinical trials prior to approval. However, this information is typically collected on an exploratory basis, and intended to inform coverage and reimbursement decisions rather than to support labeling claims in the U.S.[6] As a result, these measures may lack analytical or statistical validity, or may not be included in publications on trials results.[2]

FDA Approaches to PROs and Patient-Focused Drug Development

FDA has made substantial efforts to encourage and facilitate the use of PRO instruments in clinical drug development. The Study Endpoint and Labeling Development (SEALD) team was established within the Office of New Drugs to serve as a cross-divisional resource on clinical outcome assessments (COAs), which include PROs, clinician-reported outcomes, observer-reported outcomes, and performance measures. SEALD provides training and consultation for other review divisions on the application of measurement standards, develops agency policy related to the review, approval, and labeling of COAs, and works with a range of external stakeholders to advance the science of measurement in clinical trials.[7] The SEALD team also played a substantial role in the development of two key guidances related to PRO instrument development and use.

FDA Guidance on PROs and Qualification

In 2009, FDA published its final guidance for industry on developing PROs to support labelling claims. This document outlines the agency's current thinking around the review and evaluation of PRO instruments, and describes the recommended steps in developing an instrument, the evaluation criteria the agency will use to assess it, and the major considerations related to clinical trial design and data analysis. The agency also developed a formal, voluntary process for qualifying drug development tools (DDTs)—which include PROs as well as other COAs, biomarkers, and animal models—for use across multiple drug development programs. Guidance on this process was published in January 2014. Under the agency's definition, qualified DDTs can be relied upon to have a specific interpretation and application in the drug development and review process, provided that the tool is applied within a particular context of use.[8] Once qualified, an instrument may be applied in multiple drug development programs without the need to gather additional data to support its use. At present, the only PRO instrument to be qualified by FDA is the Exacerbations of Chronic Pulmonary Disease Tool (EXACT-PRO), which was granted qualification status in the same month that the DDT Qualification guidance was released.[9]

Patient-Focused Drug Development

As part of its commitments under the Prescription Drug User Fee Act reauthorization of 2012, the FDA has taken several steps to standardize and improve its benefit-risk assessment framework. Among these efforts is the Patient-Focused Drug Development initiative (PFDD), which began in fall of 2012. Through the PFDD, FDA will convene a series of 20 public meetings focused on specific disease areas, which will provide opportunity for patients to provide their input on the most critical aspects of their disease. FDA then hopes to build a systematic approach for incorporating this perspective into the agency's decision-making.[10] One of the potential outcomes of the PFDD is the development of PRO measures that target concepts most relevant to the patients living with these diseases.

Opportunities and Challenges in the Development and Use of PROs

Though much progress has been made in recent years by the FDA and industry to bolster PRO instrument development for labeling claims, several challenges remain. Since the introduction of the 2009 guidance, PRO label claim approvals have declined slightly, and most of the label claims granted between 2000 and 2012 were in cases where the PRO was specified as the primary endpoint, rather than as a secondary endpoint that might provide supportive data on the effects of the drug. Some have argued that this relative absence of PRO data creates a situation in which patients and prescribers have an incomplete picture of a drug's risks and benefits.[11,12]

FDA's qualification process was designed to address some of the logistical challenges associated with developing a PRO instrument or other DDT. The hope was to mitigate the associated financial and opportunity costs and take advantage of shared resources to accelerate the development of publicly available DDTs. Pre-competitive collaborations have the potential to support this process, by facilitating the development of PRO measures that can be used widely as part of drug development and evaluation research. Examples of such collaborations include the Critical Path Institute's PRO Consortium and the National Institutes of Health's Patient Reported Outcomes Measurement Information System (PROMIS). However, efforts to speed the development of qualified instruments have lagged, and only one tool has been Qualified for broader use.

The barriers to accelerating the development and use of PRO instruments stem from a range of different logistical, methodological, and communication challenges, which exist at both the industry and agency level.

Logistical barriers

Sponsors face ongoing challenges in aligning PRO development timelines with clinical development timelines, in part because they may not prioritize instrument development until the later stages of a clinical trial. Smaller companies face additional strain, as they must often contract out for PRO instrument development, creating additional logistical challenges. Applying PRO instruments in multinational clinical trials can also be a significant burden, as any changes to the instrument must be retranslated multiple times. These logistical challenges are exacerbated by the lack of harmonization for PRO instrument evidentiary requirements across regulatory agencies.

Communication barriers

Some have noted a lack of consistency across review divisions and SEALD in the interpretation of the FDA guidance.[12] Others have pointed out the structure of the review process may create additional barriers. There is no formal mechanism for meeting with FDA to discuss PRO instrument development issues prior to IND submission, and the agency's PRO experts are not embedded within clinical review divisions, which can make it difficult for sponsors to get early and consistent feedback on the PRO development plans.[13]

Methodological barriers

There are many ongoing methodological challenges associated with PRO development and use, central among them being the perceived stringency of the agency's evidentiary requirements. Some have argued that the agency should consider adjusting its criteria, particularly in regards to its standards for content validity (i.e. whether the instrument is fit for its intended purpose. [11,12] A similar challenge relates to the use of multi-domain or HRQoL measures. The agency generally encourages sponsors to pursue disease- and population-specific testing and modification for PRO instruments, but this is often a costly process for sponsors. Developing PRO instruments for pediatric, orphan, and rare disease indications present additional challenges, as do open label studies, which can be complicated by challenges related to bias from inadvertent unblinding.[11] This is particularly problematic in fields like oncology, where open label studies are common.

Meeting Objectives

In light of these issues, the Engelberg Center for Health Care Reform at the Brookings Institution, in cooperation with FDA, held an expert workshop that focused on the major issues related to the development and use of PRO instruments to support labeling claims. This workshop was the first in a series of meetings, and included representatives from across industry, academia, patient advocacy groups, and government agencies. Through these meetings, Brookings hopes to create a venue for stakeholders to identify and prioritize for action the most promising strategies to address the major barriers, and identify ways that FDA and other stakeholders can facilitate these efforts. These discussions will also help to inform a public meeting that the FDA will hold in spring 2015, which will focus on the development, use, and qualification of COAs more broadly, among other topics.

Evidentiary Standards: Balancing Methodological Rigor and Feasibility

Participants noted that the FDA guidances were important milestones in bringing methodological rigor to PRO instrument development and use. However, some expressed concern over the current interpretation and implementation of the guidances across FDA review divisions. Participants stressed the fact that evidentiary rigor must be balanced against practical feasibility, and some suggested that the evidentiary requirements, as currently applied, made the pursuit of PRO labeling claims too difficult outside of cases where the PRO instrument was supporting a primary endpoint.

Establishing the content validity of an instrument was cited as a particular challenge, owing to a range of methodological and logistical issues. Participants noted that the level of evidence required to meet FDA evidentiary standards is sometimes unclear—or is perceived as being inconsistently applied—which makes it difficult to predict the amount of time and resources that must be invested in the development of an instrument. Participants also discussed issues related to the generalizability of a given instrument across populations and disease areas. It can be difficult to determine when an instrument must be revalidated for use in a new population or sub-population, and some suggested that further empirical work be conducted to investigate these issues. Others suggested that an instrument could be considered generalizable once it has been validated in some established number of populations.

Participants also cited the challenges of aligning the instrument development process with the broader clinical development timeline. These challenges are compounded when there are delays in receiving feedback from FDA, or when reviewers request that sponsors conduct additional patient interviews—a process that can significantly impact development timelines. Participants suggested that a clearer and more consistent process for determining content validity would be helpful, and many stressed that this process should begin much earlier in the development timeline than is currently standard.

Participants also discussed the possibility of a more flexible methodological approach to instrument development and PRO data analysis, which could better reflect advances in the field of measurement science and trial design. This flexibility might also allow developers to address major methodological challenges such as missing data, multiplicity, and PRO use in open label studies. Participants cited specific examples of alternative approaches, which included mixed-methods approaches such as Group Concept Mapping, and alternative statistical analyses that could be applied to trials with multiple endpoints.

Participants also noted that an increased use of legacy instruments may represent a valuable opportunity to expand the portfolio of existing PRO instruments that FDA qualifies and accepts. Some suggested that the evidentiary standards discourage stakeholders from moving an existing measure through the qualification process, and noted that, while it took two years to develop the EXACT-PRO instrument, it took six years to get it qualified by FDA. This bias towards de novo instrument development may be leading to unnecessary duplication of effort. A clear pathway for qualifying legacy instruments might speed the development and approval of qualified PRO instruments. Participants also noted that, while more challenging to use in support of labeling claims, multidimensional instruments (such as those that capture HRQoL) are highly meaningful to patients and are increasingly accepted by the European Medicines Agency (EMA). A similar process for evaluating and accepting multidimensional measures at the FDA might be a useful.

The discussion also included consideration of the FDA's evidentiary review process, and its capacity to meet sponsor demands for timely feedback. The agency faces resource and staffing constraints, both within its review divisions and at SEALD, which may be hindering its ability to assess PRO instruments efficiently. Participants proposed that FDA consider using external reviewers, similar to the approach adopted by the EMA. In addition, the development of a training program for existing FDA staff could help to ensure that current reviewers have the appropriate experience and expertise to evaluate PRO instruments.

Participants also proposed the development of case studies of accepted and rejected PRO label claims, which could be shared publicly and would serve to illustrate the underlying principles behind FDA review decisions. Better transparency could help illuminate FDA's expectations regarding evidentiary standards, and could also help to ensure that FDA decisions are more consistent between the various review divisions and the SEALD team.

Standardizing Communication Processes Among Key Stakeholders

While the FDA encourages instrument developers to meet with them as early and as often as possible during the PRO development process, participants generally agreed that a clearer and more consistent process for engagement would be welcome. They also stressed the need for consistency in communication across review divisions and SEALD. Consistent expectations regarding evidentiary standards would be helpful, and could allow sponsors to better understand—and thus, anticipate--the level of evidence needed to obtain FDA approval and allow for more efficient advanced planning of PRO instrument development. Participants reiterated that the use of case studies would allow FDA and other stakeholders to develop a better framework of communication around other major issues surrounding PRO development, such as those related to acceptable endpoints or the use of legacy and multidimensional instruments, among others.

Participants also suggested that FDA consider additional steps to encourage sponsors to incorporate PROs earlier in the development process. For example, the agency could adopt an opt-out model to PRO use, wherein every sponsor must describe in their IND application how they intended to measures patient experience and, if they do not intend to measure this, to provide a justification for this exclusion. Participants also suggested a framework for earlier interaction with FDA—before the submission of an IND application—not just for the purpose of PRO instrument development, but also in regards to endpoint selection. A process for less formal interactions between FDA and sponsors was also posited as an alternative or supplement to the existing process for written comments, which can take several months. The Critical Path Innovation Meeting (CPIM) developed by the Center for Drug Evaluation and Research (CDER) was cited as a possible mechanism to adapt for this purpose. CPIMs provide a forum through which multiple stakeholder groups can engage with FDA around a range of methodological and technical topics

that could advance drug development.[14] FDA has noted that these meetings could be optimal for addressing issues related to clinical outcome assessments more generally, not just PROs.

Capturing the Patient Voice in Drug Development

Participants discussed a range of strategies for ensuring that the patient perspective is more consistently incorporated into drug development. One approach would be a more streamlined process for qualifying instruments for broader use. The PRO Consortium was established with this specific goal in mind, and has significant potential to accelerate this process. However, there have been numerous implementation challenges since its inception. It can be difficult, for example, to ensure that the right participants are at the table, and negotiating contractual agreements can be time-consuming. Practicing shared decision-making and coordinating across organizations with sometimes divergent interests adds to that challenge. As the Consortium continues its work to accelerate the development of qualified instruments, it will be necessary to consider ways to make the process more efficient, both within the Consortium and the FDA. Collaboration with a broader range of stakeholders—such as the NIH's PROMIS network—could help to facilitate this process.

The experience of qualifying the EXACT-PRO instrument may also provide some insight into ways that the qualification process can be adapted. For example, while the instrument itself was developed in two years, it took six years to generate enough clinical evidence for FDA qualification. One approach for expediting the process, which the Agency has already adapted, is qualifying instruments for exploratory purposes. The requisite clinical data for qualifying the instrument for primary or secondary endpoints may then be developed over time. Participants also suggested that a clear decision tree could help to inform sponsors when the qualification of an instrument is appropriate, and when each stage of the qualification process can be considered complete. Participants also noted the advantage of starting with a legacy instrument when selecting targets for qualification.

The discussion also included approaches to accessing diverse patient populations, as well as the benefits of engaging them earlier in the drug development process. This can be challenging for a variety of reasons. Such patients may not be well-connected to the research community, and thus unaware of the possibility of participating in clinical research. They may also be too young to make informed decisions about their participation, among other barriers. However, participants stressed the fact that patients have a potential role to play across the entire drug development spectrum, from developing initial research questions, to identifying outcomes of interest, to assessing the benefits and risks of new treatments. Participants further noted that technology has a potential role to play in addressing these barriers, through web-based platforms that connect patients to ongoing research projects, for example, or phone applications that can be used to collect data.

The discussion also included consideration of the challenges in capturing the patient voice across multinational settings. These challenges are both methodological and logistical. On the logistical side, it can be difficult to implement an instrument across multiple research sites, and there are ongoing methodological challenges in accounting for cross-cultural differences in subjective concepts. More work is required to address these uncertainties.

Next Steps

Moving forward, there are a number of steps that FDA and other stakeholders might consider taking to advance the discussion around PRO instrument development and use. The following areas were prioritized for follow-up in future Brookings meetings:

Identification of Acceptable Endpoints

The SEALD team is currently collaborating with each of the Office of New Drugs review divisions to identify endpoints that, while not yet fully qualified, are currently considered potentially acceptable for use in particular therapeutic areas. The agency will then publish this information, along with a description of the context in which these instruments would be appropriate for primary or secondary endpoints. The agency will consider the utility of identifying which instruments are not considered acceptable, and gaps in these measures that would need to be addressed before they could be used in a clinical trial for regulatory purposes. In advance of this publication, FDA will seek input from stakeholders on its approach to collecting these data, and identify strategies for communicating the information to drug developers.

Adapting Fit-For-Purpose Legacy Instruments

In some cases, there may be existing instruments that could be adapted to make them fit for purpose in a given context. However, there are a number of scientific and communication issues that will need to be identified and resolved in order to streamline the process for adapting legacy instruments. For example, what level of evidence is necessary to determine that select domains from legacy measures are acceptable? What level of evidence is required to adapt an existing accepted instrument to a new population? How can the risk of using a particular instrument be mitigated and communicated to sponsors in cases where there is insufficient evidence of the instrument's validity, reliability, and ability to detect change? FDA will seek input from stakeholders on these and a range of other questions related to adapting legacy instruments.

Streamlining CDER Review and Communication Processes

The process for qualifying an instrument is very specific and detailed, and often requires considerable time and resources to complete. While pre-competitive collaboration is a key strategy for cost-sharing, such collaborations do not necessarily reduce the timeline, owing to lengthy contract negotiation procedures, the need to build consensus, and the time required for FDA review and feedback. The process for consulting with FDA within the context of an individual drug development program can also be time-consuming, and may discourage industry use of PROs outside of cases where the instrument supports a primary endpoint. FDA will seek further input on strategies that might help to improve the efficiency and clarity of their process for engaging with industry around instrument development, use, and qualification.

Building a PRO Research Agenda

Participants in the meeting noted that there are many outstanding methodological questions that have hindered the development and use of PRO assessments to support labeling claims (e.g., the use of PROs in open label studies, the cross-cultural adaptation of instruments in multinational trials). The agency will consult with academic thought leaders and other stakeholders on developing a research agenda that will identify and prioritize for action those research questions that have hindered interpretation of PRO assessments.

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