VALUE IN HEALTH 21 (2018) 967–972

Available online at www.sciencedirect.com

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journal homepage: www.elsevier.com/locate/jval

Patient-Reported Outcomes

Patient-Reported Outcome Measures in the Food and Drug Administration Pilot Compendium: Meeting Today's Standards for Patient Engagement in Development?

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ABSTRACT

Background: In 2016, the Food and Drug Administration (FDA) released a Pilot Clinical Outcome Assessment Compendium (COA Compendium) intended to foster patient-focused drug development (PFDD). However, it is unclear whether patient perspectives were solicited during development or validation of the included patient-reported outcome (PRO) measures. **Objective:** To examine the pedigree of a sample of measures included in the COA Compendium. **Methods:** PROs included in chapters 1 or 2 of the COA Compendium were extracted and three reviewers independently searched PubMed and Google to identify information on measure pedigree. Data on method and stage of measure development where patient engagement took place were documented. **Results:** Among the 26 evaluated PRO measures, we were unable to identify information on development or validation on nearly half the sample (n = 12). Among the remaining 14 measures, 5 did not include any evidence of patient engagement; 2 engaged patients during concept elicitation only; 1 engaged patients during psychometric validation only; and 6 engaged patients during both concept elicitation and cognitive interviewing. Measures either previously qualified or submitted for qualification were more likely to include patient engagement. **Conclusions:** For the FDA Pilot COA Compendium to fulfill its purpose of fostering PFDD, it needs fine-tuning to reflect today's standards, improving transparency and facilitating clear identification of included measures so that the level of patient engagement, among other factors, can be properly assessed. Suggested improvements include identifying clinical trials that correspond to the COA Compendium's use in drug development; more clearly identifying which measure is referred to; and including only those measures that already qualified or undergoing qualification.

Keywords: Clinical Outcome Assessment (COA), Patient-focused drug development (PFDD), Patient Engagement [Method], Measure Development.

Introduction

Over the past decade, the US Food and Drug Administration (FDA) has led a movement to improve the validity and relevance of clinical outcome assessment (COA) tools to support labeling [1]. To help drug and COA instrument developers navigate these changes, the FDA published a "Roadmap to Patient-Focused Outcome Measurement in Clinical Trials," along with the 2009 Guidance on Patient-Reported Outcomes (PROs) [2,3]. Adherence to the guidance improves the likelihood that COAs (PROs, clinician-reported outcomes, observer-reported outcomes, and performance outcomes) used to measure treatment benefit in drug approval trials will identify meaningful treatment benefit (e.g., how a patient survives, feels, or functions) as defined by patients [2]. They also promote rigorous methodology in developing and validating COAs by describing FDA considerations on content validity and reliability, among others.

In 2016, the FDA released a Pilot Clinical Outcome Assessment Compendium (COA Compendium) [4]. The COA Compendium is a list of COAs used as primary or secondary end points in trials and discussed in product labels between 2003 and 2014. The COA Compendium is part of FDA's efforts to "foster patient-focused drug development (PFDD) by collating and summarizing COA information for many different diseases and conditions into a single resource intended to: (1) facilitate communication; (2) provide clarity and transparency; and (3) be used as a starting point for early drug development" [5–7]. It seeks to help drug developers overcome some of the logistical barriers related to including COAs in clinical trials, particularly in identifying existing measures or measures that could be modified on the basis of context of use [2].

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1098-3015$36.00 – see front matter

https://doi.org/10.1016/j.jval.2018.01.004

Table 1 – FDA-Identified key considerations of the COA Compendium [4].

- "The COA Compendium (PDF) is not a comprehensive list of clinical outcome assessments and is not intended to replace either existing disease-specific guidance or key interactions with FDA concerning drug development (e.g., during pre-IND meetings). Inclusion of a clinical outcome assessment in the COA Compendium is not intended to indicate that the measure is or should be the sole (or primary) determinant of a clinical benefit in a clinical trial."
- "Drug sponsors are strongly encouraged to seek advice from the relevant Office of New Drug (OND) review division early in drug development to discuss the selection and implementation of the clinical outcome assessment specific to their program, irrespective of whether the disease, condition, indication, claim, or clinical outcome assessment is included in the COA Compendium."
- "Some of the clinical outcome assessments listed in the COA Compendium may be protected by proprietary rights, and in some cases, a royalty and fee may be charged by the copyright owners for their authorized use. The inclusion of a clinical outcome assessment in the COA Compendium does not equate to an endorsement by FDA."

COA, clinical outcome assessment; FDA, Food and Drug Administration.

Despite FDA's disclaimers on what the COA Compendium includes and does not include (see Tables 1 and 2), the COA Compendium may be perceived as an endorsement of included measures [1]. Given the time frame of COAs eligible for inclusion in the COA Compendium, many are likely to predate the December 2009 release of FDA's Guidance on PRO Measures to Support Labeling Claims [3]. There are concerns that the COA Compendium includes measures that would not be accepted as a well-defined and reliable assessment of a specified concept of interest. Furthermore, although the COA Compendium is intended to "foster patient-focused drug development," there are concerns that COA Compendium-listed measures do not measure a concept of interest that reflects outcomes that matter to patients. Indeed, with the exception of just two measures (Evaluating Respiratory Symptoms in Chronic Obstructive Pulmonary Disease [E-RS: COPD] and Exacerbations of Chronic Pulmonary Disease Tool [EXACT]), the rest of the measures included in the COA Compendium have not gone through the formal COA qualification process and references to published validation studies are not included in the COA Compendium [4]. While measures can be well developed and suitable for the assessment of treatment benefit without undergoing FDA's qualification program, for example, COAs developed as part of an individual drug development program, data on these measures are not required to be made publicly available. Thus, measure developers may or may not have followed the 2009 guidance or provide sufficient information to document validity or reliability.

Furthermore, there is no documentation included in the COA Compendium on the level of patient engagement in the development of any of the included measures. With heightened awareness of the need for patient engagement in all aspects of health care and research, it would inform use and interpretation to understand whether the PRO measures included in the COA Compendium were grounded with patient input from inception. To better understand the pedigree of measures listed in the COA Compendium and to gauge its potential contribution to PFDD, this scoping review attempted to identify when and how patients were engaged during the development of a sample of PRO measures included in the COA Compendium.

Scoping Review Methods

COA measures included in either the COA Compendium's first (Office of Microbial Products) or second (Office of Drug Evaluation I) chapter were stratified by type of COA (clinician-reported outcome, observer-reported outcome, PRO, or performance outcome). These chapters were selected to cover a broad range of products including anti-infective, antiviral, transplant, ophthalmology, cardiovascular, renal, neurology, and psychiatry. The list of PROs was extracted from the COA Compendium chapters as the study sample. Three reviewers independently searched PubMed and Google to identify information on the origins and validation of these PRO measures. Searches were conducted between February and July 2017.

To identify patient engagement activities, reviewers were instructed to look for any information related to the following: How was concept elicitation operationalized? Was cognitive debriefing mentioned? If yes, how was it operationalized? Were patients involved as test subjects only? Reviewers were also asked to document any other information pertinent to understanding how the measure was developed or validated, especially with regard to patient involvement.

The first two reviewers captured all information in a data extraction template, which was then verified by a third researcher, an expert in PRO development and validation, through repetition of the scoping review methods. If patient engagement was noted to have taken place, data on patient engagement method used and stage of measure development where patient engagement took place were documented and all sources were cataloged and recorded to facilitate comparisons between reviewer findings [8]. Discrepancies in intercoder reliability were addressed through data triangulation

Table 2 – FDA-Identified limitations associated with the COA Compendium [32].

- "The COA Compendium is not a comprehensive list of all medical conditions or clinical outcome assessments that could potentially support labeling claims.
  - It should be underscored that the current pilot version of the COA Compendium is limited in scope—that is, it is primarily based on the retrospective review of NME labeling approved from 2003 to 2014 and excludes all efficacy supplements.
  - Clinical outcome assessments not included in the COA Compendium should also be considered during drug development, as appropriate, especially those supported by data, literature, and good measurement principles.
- The COA Compendium is not a replacement for interactions with appropriate FDA review divisions nor does it supersede existing disease-specific guidance. For example:
  - The COA Compendium omits critical aspects of how a listed clinical outcome assessment could be implemented in a clinical trial (e.g., clinical trial design).
  - Inclusion of a clinical outcome assessment in the COA Compendium is not intended to indicate that the measure is or should be the sole determinant of a clinical benefit in a clinical trial. Other assessments, such as overall survival, may be critical drivers of establishing efficacy or clinical benefit.
  - End-point hierarchy and selection of key outcome assessments are always specific to the context of a drug candidate in a therapeutic area and should be discussed with the appropriate review division prior to initiating clinical trials."

COA, clinical outcome assessment; FDA, Food and Drug Administration.