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REVIEW

Considerations in the Assessment of Clinical Benefit with a Focus on Pain: a Regulatory Perspective

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Abstract
In the USA, the regulatory standard for demonstration of efficacy of a drug is evidence of clinical benefit from adequate and well-controlled clinical trials. Understanding the natural history of disease and how treatment is expected to alter its course, and gathering input from relevant stakeholders, such as patients, caregivers, and clinicians, is essential to understand the best way to measure clinical benefit in a clinical trial. Though pain intensity has been the primary outcome measure in clinical trials for pain, an array of measures assessing clinical outcomes from multiple perspectives can allow for more comprehensive interpretation of how a treatment affects patients' lives. Careful consideration should be given to how pain affects the feeling and functioning of each distinct patient population and which outcome assessment, or combination of outcome assessments, may be necessary to provide a more comprehensive view of the patient experience. The early stages of medical product development are an important opportunity to engage with regulatory agencies to discuss potential approaches to clinical trial design and outcome measurement strategies.

Key Words FDA · outcome · measurement · trials · pain

Introduction

A fundamental goal of a clinical trial is to evaluate the clinical benefit of an intervention on the disease or condition of interest. In the context of most clinical trials, FDA's perspective is that clinical benefit means that the intervention produces a positive, clinically meaningful effect on how a patient feels, functions, or survives. In the USA, the regulatory standard for demonstration of efficacy of a drug is evidence of clinical benefit from adequate and well-controlled clinical trials [1]. Generation of evidence is based on the results of trial endpoints, which generally fall into two categories: clinical endpoints and surrogate endpoints. Clinical endpoints measure or reflect how patients feel, function, or survive and rely on use of clinical outcome assessments. Given that pain is a uniquely subjective and individual experience, clinical outcome assessment informed by patient and caregiver input is key to the understanding and evaluation of pain. In this paper, we focus on strategies for assessment of clinical benefit in medical product development highlighting certain considerations in pain.

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Laying the Foundation for Assessing Clinical Benefit

Understanding the Disease or Condition and Patient Subpopulations

At the early stages of planning for clinical studies—even prior to selecting potential endpoints and endpoint measures—it is important to consider the target patient population for drug development as well as potential clinical benefit(s) of the treatment. Early considerations in assessment of clinical benefit include understanding the natural history of the disease and how treatment is expected to alter its course. Factors such as disease onset and time to diagnosis, clinical course of symptoms (e.g., acuity/chronicity, time course of symptoms, intermittent or continuous onset and duration), and heterogeneity of clinical manifestations should guide selection of

measurable concepts (i.e., aspects of an individual's clinical, biological, physical, or functional state, or experiences that the assessment is intended to capture or reflect [2]) that are expected to change as a result of treatment within the time frame of a clinical trial. For example, an increasing body of evidence shows that patients with low back pain vary in the course of progression and it is thought that a better understanding of this patterns of progression (e.g., from acute to subacute to chronic pain) may allow for identification of novel targets for therapeutic intervention [3]. Understanding the course and temporal characteristics of pain may also improve its measurement by selecting clinical outcome assessments and an assessment schedule most apt to capture the patient experience. Additionally, in planning for measurement in diverse patient populations, understanding patient subpopulations of interest includes understanding other sources of heterogeneity that may arise. For example, it has been reported in several studies that certain subpopulations (e.g., older adults or individuals with cognitive impairment) may report greater difficulty with some types of pain scales compared with others [4–6].

Listening to Stakeholders

Understanding the disease or condition includes understanding the patient experience. Input from relevant stakeholders (e.g., patients, caregivers, clinicians, disease experts) is essential to understand which concepts are most impactful on daily living and most important to treat and to understand the best way to measure clinical benefit. For example, stakeholder input can be gathered to help elucidate whether it is most meaningful and informative to measure frequency of symptoms, intensity of symptoms, impacts of symptoms, and/or another aspect of the patient experience. Stakeholder input can also add to the understanding of what level of change in signs or symptoms may be considered meaningful.

The FDA recognizes that patients with chronic disease are experts in what it is like to live with their condition and are well-positioned to inform unmet needs for therapeutics and meaningful concepts for assessment in clinical trials. As part of the FDA's Patient-Focused Drug Development (PFDD) initiative, the agency has hosted a number of disease-specific public meetings in chronic diseases with patients and caregivers [7], each of which has resulted in the posting of a summary report, which can serve as a valuable resource for understanding unmet needs in drug development and aspects of importance to patients for potential measurement in clinical trials. These have included a meeting in the area of chronic pain [8], neuropathic pain associated with peripheral neuropathy [9], fibromyalgia [10], and a number of other diseases associated with pain [7]. Although the experience of pain is highly individual, some common themes have emerged shedding light on the complex ways chronic pain impacts patients' lives and potential concepts to be assessed in clinical trials. These include the impact of pain on sleep, associated fatigue, and the impact of chronic pain on physical, social, and emotional functioning, among other domains. The complex interrelationship of pain and fatigue, pain and physical functioning, and pain and depression are well-recognized highlighting the meaningfulness of these associated concepts as targets for measurement. Beyond patient stakeholders, input from a host of other stakeholders, including regulators, drug developers, clinicians, measurement experts, disease experts, and others, is needed to inform and prioritize targets for measurement and measurement tools.

Formulating a Measurement Strategy

Selecting or developing clinical outcome assessments and their associated endpoints for use in drug development is not necessarily a linear process, but rather an iterative one that necessitates multiple simultaneous considerations. Meeting with regulatory agencies early in the drug development process, and frequently throughout, is recommended to maximize the opportunity to collect high-quality data necessary to facilitate regulatory decision-making. The following sections should not be viewed strictly as step-by-step process for formulating a measurement strategy, but rather serve to illustrate a few of the many factors to be considered throughout the course of medical product development.

Identifying Types of Clinical Outcome Assessments

As is the case with chronic pain, for example, it is common for multiple concepts to be considered meaningful, so clinical trials commonly use multiple endpoint measures. Given the complex interplay of pain and its impacts, various concepts can be targeted in the endpoint hierarchy, with prioritization of concepts most likely to demonstrate change with the intervention as well as most meaningful. Selection of the appropriate type of clinical outcome assessment, or combination of clinical outcome assessments, requires consideration of which type of respondent—patient, caregiver, or clinician—is likely to be most adequately equipped to report on the specific clinical outcome of interest. For concepts (e.g., symptoms) that can be most validly and reliably reported directly from the patients, a patient-reported outcome measure is appropriate; if clinical judgment is required, then a clinician-reported outcome measure may be appropriate; if observable behaviors in daily life are being assessed, and if the patient cannot validly and reliably self-report, then an observer-reported outcome measure may be appropriate; and if demonstration of a patient's functional performance on a defined task is useful, then a performance outcome measure (e.g., standardized tests of ambulation or cognition) may be considered [2]. Digital health technology tools, such as wearable activity-

monitoring devices, are also increasingly being explored in clinical trial contexts [11].

In the context of clinical trials for pain, pain intensity has been the primary outcome measure. Because pain intensity is representative of how a patient feels, it is best reported directly by the patient using a patient-reported outcome measure, if the patient can reliably self-report. Measurement of functional concepts related to impacts of pain, including physical functioning and emotional functioning, can provide additional context surrounding the effects of treatment on patient outcomes. The Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT), a consortium of representatives from academia, regulatory authorities, patient advocacy organizations, health systems, and the pharmaceutical industry, has recommended that pain intensity be the primary measure of clinical trials for chronic pain and that physical, emotional, and social functioning also be assessed to inform how patients feel and function in their daily lives, using patient input to inform measurement of relevant and meaningful concepts from the patient perspective [12, 13]. Assessment of patient-identified impacts of pain-related conditions on daily functioning has supported drug labeling claims, such as measurement of disease impacts on aspects of daily living in patients with migraine [14, 15]. Evidence of patient input to support relevance and meaningfulness of clinical outcome assessments is an important component of FDA review of proposed labeling claims [16].

An array of measures assessing clinical outcomes from multiple perspectives can allow for more comprehensive interpretation of how a given medical product affects patients' lives. For example, if physical functioning is the concept of interest, then an endpoint based on a PRO assessment could be used to measure a patient's self-reported physical functioning in his or her daily life, and an endpoint based on a performance outcome assessment could provide additional information based on performance of a task administered by a clinician. In addition, there is interest in use of digital health technology tools (e.g., wearable sensors) in monitoring physical activity in patients with chronic musculoskeletal pain in clinical trials. Such tools provide passive measurements of patients' movement in their "natural environment" (e.g., home, work, school) and may provide complementary information to other clinical outcome assessments (e.g., patient-reported outcome measures of pain intensity and physical functioning).

Considerations in Specific Populations

Some disease-related concepts, such as pain intensity, are only known by the patient and cannot be validly and reliably reported by a caregiver or clinician. For situations in which patients in the target population are expected to be unable to reliably self-report, then an assessment by a caregiver or other observer based purely on clearly defined, observable signs could be used. Observable signs of pain, such as the patient grimacing, rubbing the affected area, or vocalizing responses to pain (e.g., "it hurts"), can be reported using an observer-reported outcome measure.

Importantly, observer reporting is not synonymous with proxy reporting; the former relies only on measurement of observable signs, whereas the latter requires the proxy reporter to assess the patient's symptoms on behalf of the patient. An example of proxy reporting is a caregiver or clinician reporting on how intense a young child's pain is on a scale from 0 to 10, without the child directly reporting a numeric rating. Proxy reporting is considered inherently unreliable for regulatory purposes, as it is not possible for the proxy reporter to truly know how the patient feels. Therefore, the FDA Guidance for Industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims* [16] discourages the use of proxy-reported outcome measures particularly for symptoms that can be known only by the patient.

Pain measurement continues to be a challenge in patients who are unable to self-report, such as measurement of pain in young children and nonverbal patients. Although caregiver-reported or clinician-reported assessments of observable signs of pain are facilitated in children who are developmentally able to distinguish and verbalize feelings of pain from other forms of distress or discomfort (e.g., hunger), it is less clear how to best identify and rate pain *versus* nonpain distress in infants and young children. In 2019, as part of a pilot grant program under the FDA PFDD initiative, the FDA awarded the Duke Clinical Research Institute to develop a core set of clinical outcome assessments and related endpoints for use in clinical trials of acute pain therapeutics in children aged 2 years and younger [17].

Conclusions

Development of an effective outcome measurement strategy involves understanding of the medical product, the disease state of interest, and the targeted patient population. Though pain is a prevalent concept across many therapeutic areas, and established measures of pain intensity are well-known, careful consideration should be given to how pain affects the feeling and functioning of each distinct patient population, and which outcome assessment, or combination of outcome assessments, may be necessary to provide a more comprehensive view of the patient experience.

The early stages of medical product development are an important opportunity to engage with regulatory agencies to discuss potential approaches to clinical trial design and outcome measurement strategies. The FDA Guidance for Industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims* [16] can serve as a reference regarding development and use

of clinical outcome assessments and evidence needed to support regulatory decision-making, and resources from the FDA PFDD initiative can help to facilitate incorporation of stakeholder input into the drug development process [7, 16, 18]. Consultation and advice from regulatory agencies on clinical outcome assessments (existing or to-be-developed) can also be sought outside the context of a specific drug development program (e.g., within CDER's Drug Development Tool Qualification Program) [19]. Ongoing collaboration with regulators is encouraged to facilitate development of assessment strategies and tools that advance the science of pain measurement and address unmet needs.

Required Author Forms Disclosure forms provided by the authors are available with the online version of this article.

Compliance with ethical standards

Disclaimer This article reflects the views of the authors and should not be construed to represent FDA's views or policies.

References

1. CFR Title 21 §314.126.b.6.
2. FDA-NIH Biomarker Working Group. BEST (Biomarkers, EndpointS, and other Tools) Resource: National Institutes of Health; 2016 [cited January 22, 2020]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK338448/.
3. Gatchel RJ, Bevers K, Licciardone JC, Su J, Du Y, Brotto M. Transitioning from acute to chronic pain: an examination of different trajectories of low-back pain. Healthcare (Basel). 2018;6(2):48.
4. Dworkin RH, Turk DC, Farrar JT, Haythornthwaite JA, Jensen MP, Katz NP, et al. Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. Pain. 2005;113(1-2):9-19.
5. Williamson A, Hoggart B. Pain: a review of three commonly used pain rating scales. J Clin Nurs. 2005;14(7):798-804.
6. Hjermstad MJ, Fayers PM, Haugen DF, Caraceni A, Hanks GW, Loge JH, et al. Studies comparing Numerical Rating Scales, Verbal Rating Scales, and Visual Analogue Scales for assessment of pain intensity in adults: a systematic literature review. J Pain Symptom Manage. 2011;41(6):1073-93.
7. U.S. Food and Drug Administration. The voice of the patient: a series of reports from FDA's Patient-Focused Drug Development Initiative 2019 [cited February 13, 2020]. Available from: https://www.fda.gov/industry/prescription-drug-user-fee-amendments/voice-patient-series-reports-fdas-patient-focused-drug-development-initiative.
8. U.S. Food and Drug Administration. The voice of the patient: chronic pain 2019 [cited February 13, 2020]. Available from: https://www.fda.gov/media/124390/download.
9. U.S. Food and Drug Administration. The voice of the patient: neuropathic pain associated with peripheral neuropathy 2017 [cited February 13, 2020]. Available from: https://www.fda.gov/media/103149/download.
10. U.S. Food and Drug Administration. The voice of the patient: fibromyalgia 2014 [cited February 13, 2020]. Available from: https://www.fda.gov/media/90052/download.
11. Dashiell-Aje E, Kovacs S, Sacks L. Digital health technology tools: use in clinical investigations to evaluate clinical benefit in patients. DIA Global Forum. 2019 (June 2019).
12. Turk DC, Dworkin RH, Allen RR, Bellamy N, Brandenburg N, Carr DB, et al. Core outcome domains for chronic pain clinical trials: IMMPACT recommendations. Pain. 2003;106(3):337-45.
13. Taylor AM, Phillips K, Patel KV, Turk DC, Dworkin RH, Beaton D, et al. Assessment of physical function and participation in chronic pain clinical trials: IMMPACT/OMERACT recommendations. Pain. 2016;157(9):1836-50.
14. U.S. Food and Drug Administration. Drug Approval Package: Aimovig (Erenumab-aooe) Injection. Silver Spring, MD: U.S. Food and Drug Administration; 2018 [updated June 14, 2018; cited 2020 June 11, 2020]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/761077Orig1s000TOC.cfm.
15. U.S. Food and Drug Administration. Emgality (Galcanezumab-gnlm). Silver Spring, MD: U.S. Food and Drug Administration; 2018 [updated November 7, 2018; cited 2020 June 11, 2020]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/761063Orig1s000TOC.cfm.
16. U.S. Food and Drug Administration. Guidance for Industry: Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims 2009 [cited January 22, 2020]. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/patient-reported-outcome-measures-use-medical-product-development-support-labeling-claims.
17. U.S. Food and Drug Administration. CDER Pilot Grant Program: Standard Core Clinical Outcome Assessments (COAs) and Their Related Endpoints 2019 [cited January 22, 2020]. Available from: https://www.fda.gov/drugs/development-approval-process-drugs/cder-pilot-grant-program-standard-core-clinical-outcome-assessments-coas-and-their-related-endpoints.
18. U.S. Food and Drug Administration. FDA Patient-Focused Drug Development Guidance Series for Enhancing the Incorporation of the Patient's Voice in Medical Product Development and Regulatory Decision Making 2019 [cited February 13, 2020]. Available from: https://www.fda.gov/drugs/development-approval-process-drugs/fda-patient-focused-drug-development-guidance-series-enhancing-incorporation-patients-voice-medical.
19. U.S. Food and Drug Administration. Drug Development Tool (DDT) Qualification Programs 2020 [cited February 13, 2020]. Available from: https://www.fda.gov/drugs/development-approval-process-drugs/drug-development-tool-ddt-qualification-programs.