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CLIENT ALERT

FDA Calls for Comments on Its Extensive Draft Guidance on Use of Patient-Reported Outcome Instruments in Medical Device Lifecycle Analysis

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The U.S. Food and Drug Administration (FDA or the Agency) is seeking comments on extensive new guidance intended to further integrate patient input throughout the product lifecycle of medical devices. FDA is encouraging the collection, analysis, and integration of patient perspectives in the development and evaluation of medical devices, and notes that patients' perspectives on living with their health condition and its treatment or management are most useful in medical device evaluation when relevant to the regulatory decision and reliably measured. The Agency has outlined recommendations to help ensure that patient-reported outcome (PRO) instruments are fit for purpose and configured in a way that generates relevant, reliable, and sufficiently robust data for use in assessing outcomes throughout the regulatory process.

See Principles for Selecting, Developing, Modifying, and Adapting Patient-Reported Outcome Instruments for Use in Medical Device Evaluation – Draft Guidance for Industry and Food and Drug Administration Staff, And Other Stakeholders*, available at* https://www.fda.gov/regulatory-information/search-fda-guidance-documents/principles-selecting-developing-modifying-and-adapting-patient-reported-outcome-instruments-use.

PRO instruments facilitate the collection of data—including narrative or metric evidence documenting how patients feel, function, and survive—to support both regulatory and healthcare decision-making. Such instruments are able to produce valid scientific evidence of safety and effectiveness that is complimentary to other evidence and/or clinical outcomes or biomarkers, and may be specifically recommended in certain standards and guidance. PRO instruments take many forms, and may include diaries, visual analog scales (*e.g.*, pain severity), symptom measures, and questionnaires. Compared to standard success metrics, PRO instruments seek to reflect the patients' thoughts, and may be measured by self-report or through interviews recording only the patients' responses. In this way, PRO instruments are able to measure symptoms and unobservable outcomes known only to the patient (*e.g.*, pain or anxiety levels). Within FDA's process, use of PRO instruments has been generally voluntary, but this guidance cements FDA's willingness to further integrate PRO instruments into the regulatory submission process.

Previously, FDA has produced several resources to assist a device sponsor in selecting, modifying, or developing a PRO instrument,[1] and PRO instruments have been qualified under the Medical Device Development Tools (MDDT) program—meaning that the Center for Devices and Radiological Health (CDRH) has evaluated the tool and concurs with available supporting evidence that the PRO produces scientifically plausible measurements and works as intended within the specific context of use. Commensurate with this trend, the Agency has indicated that information

from well-defined and reliable PRO instruments can provide valuable evidence for benefit-risk assessments and can be used in medical device labeling to better communicate the effect of a treatment on patient symptoms, functioning, and health-related quality of life (where validated). Moreover, PRO instruments may be used to help determine a patient's eligibility for inclusion within a study, to measure primary or secondary safety, and/or effectiveness endpoints.

By integrating patients' voices throughout the total product lifecycle, concepts important to patients can be considered in the evaluation and surveillance of medical devices. In this draft guidance, FDA has indicated that the following principles should be considered when incorporating PRO instruments into the evaluation of a medical device across its lifecycle:

1. establish and define the concept of interest (COI) the PRO instrument is intended to capture;
2. clearly identify the role of the PRO (*e.g.*, primary, key secondary, or exploratory) in the clinical study protocol and statistical analysis plan;
3. provide evidence showing that the PRO instrument reliably assesses the COI; and
4. effectively and appropriately communicate the PRO-related results in the labeling to inform healthcare provider and patient decision-making.

FDA believes that PRO instruments that are fit-for-purpose should be used for a specific context of use (COU) and that the following three factors should be considered when selecting a PRO instrument:

1. Is the concept being measured by the PRO instrument meaningful to patients and would a change in the COI be meaningful to patients?
2. What role will the PRO instrument serve in the clinical study protocol and statistical analysis plan?
3. Does the evidence support its use in measuring the COI as specified in the clinical study protocol and statistical analysis plan?

FDA has also shared "Best Practices for Least Burdensome Selection, Development, Modification and Adaption of Patient-Reported Outcome Instruments," suggesting that device sponsors:

- **Measure concepts important to patients** by incorporating outcomes that reflect patient priorities in the clinical study protocol through effective patient engagement, concept elicitation interviews,[2] and cognitive interviews during PRO instrument development, which can help ensure that the COIs intended to be measured by a PRO instrument are important to the daily lived experiences of patients and could be useful to inform their future decisions regarding the use of the medical device.
- **Ensure PRO instruments are understandable to patients** by drafting necessary instructions, items, recall period, and response options in plain language; utilizing appropriate benchmarks, activities, or symptom wording; and conducting cognitive interviews to generate evidence supporting the language of PROs. FDA also recommends offering PRO instruments in different languages, where appropriate, in order to measure the patient experiences in patients with limited English-language proficiency and health literacy.
- **Be clear about the role of PRO instruments in the clinical study protocol and statistical analysis plan** by properly defining the COI, including a statement of what is being measured, how it is being measured and interpreted, and how the results will be communicated in the labeling; by drafting a COU that describes the specific role of the PRO instrument in the development and evaluation of the medical device and plainly stating the instrument's COU in the clinical study protocol; and by engaging FDA during the study-design stage.
- **Leverage existing PRO instruments and validity evidence** by modifying existing PRO instruments where applicable, appraising peer-reviewed literature to identify validity evidence, and engaging in discussion with FDA through the Q-submission process.[3]
- **Consider alternative platforms and parallel development for generating validity evidence for PRO instruments** by and through the use of real-world evidence obtained from electronic health records, claims and

billing activities, patient-driven registries, and health-monitoring devices, among others.

- **Collaborate with others in the pre-competitive space,** where possible and appropriate, by working together with relevant stakeholders, health professional organizations, and research institutions (among others) to develop, modify, or adapt a PRO instrument for use in regulatory submissions.

The Agency believes the recommendations outlined above will help ensure that PRO instruments are developed, modified, adapted, or used in the evaluation of medical devices in a way the generates relevant, reliable, and sufficiently robust data to assess outcomes of importance to patients, regulators, and healthcare providers while providing flexible approaches to doing so.

We note that government orders on the local, state, and federal level are changing every day, and the information contained herein is accurate only as of the date set forth above.

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For further information or questions on FDA's guidance and the use of PROs in medical device development, please contact Amandeep S. Sidhu, T. Reed Stephens, Christopher Parker, or your Winston relationship attorney.

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[1] These include the guidance entitled "Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims"; a series of guidance documents and other resources related to Patient-Focused Drug Development, *available at* https://www.fda.gov/drugs/development-approval-process-drugs/fda-patient-focused-drug-development-guidance-series-enhancing-incorporation-patients-voice-medical; and the following resources: "Value and Use of Patient-Reported Outcomes (PROs) in Assessing Effects of Medical Devices," and "PRO Compendium."

[2] Concept elicitation is a process to collect a holistic set of relevant concepts that are important to patients.

[3] FDA's Q-Submission Program provides submitters opportunities to have early collaboration and discussions regarding their medical device submissions and discuss issues communicated by FDA during review of other submission types.

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Amandeep S. Sidhu

T. Reed Stephens

Christopher M. Parker