AdvaMed
Advanced Medical Technology Association

701 Pennsylvania Avenue, NW
Suite 800
Washington, D.C. 20004–2654
Tel: 202 783 8700
Fax: 202 783 8750
www.AdvaMed.org

October 28, 2020

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

RE: Docket No. FDA–2020–D–1564: Principles for Selecting, Developing, Modifying, and Adapting Patient Reported Outcome Instruments for Use in Medical Device Evaluation; Draft Guidance for Industry, Food and Drug Administration Staff, and Other Stakeholders; Availability

Dear Sir or Madam:

The Advanced Medical Technology Association ("AdvaMed") is pleased to provide comments on the Food and Drug Administration's (FDA's or "Agency's") draft guidance entitled "Principles for Selecting, Developing, Modifying, and Adapting Patient Reported Outcome Instruments for Use in Medical Device Evaluation."

The Advanced Medical Technology Association (AdvaMed) is the world's largest trade association representing medical device and diagnostics manufacturers. AdvaMed's member companies produce the innovations that are transforming health care through earlier disease detection, less invasive procedures and more effective treatments. AdvaMed has more than 400 member companies, ranging from the largest to the smallest medical technology innovators and manufacturers. AdvaMed advocates for a legal, regulatory and economic environment that advances global health care by assuring worldwide patient access to the benefits of medical technology. The Association promotes policies that foster the highest ethical standards, rapid product approvals, appropriate reimbursement, and access to international markets.

AdvaMed has general and specific comments on the draft guidance below.

General Comments

AdvaMed supports the development of the draft Patient Reported Outcome (PRO) instruments guidance as a step toward meeting the MDUFA V Commitment Letter, specifically F. 3. B. However, as noted in our specific comments below, the guidance should be strengthened to include examples of least burdensome ways in which existing broad PRO instruments can be used for other subpopulations without having to conduct cognitive debriefing or validation. Given the cost and time associated with revalidating PRO instruments, we also recommend that the guidance include several examples of the

types of modifications that would or would not require revalidation of the PRO instrument for cohorts that differ from the original PRO instrument cohort as well as other modifications that may be appropriate to implement to an existing PRO instrument without extensive re-validation of the entire instrument.

Specific Comments
AdvaMed's specific comments are attached in table format below.

In closing, thank you for the opportunity to provide comments on FDA's draft guidance on Principles for Selecting, Developing, Modifying and Adapting Patient Reported Outcome Instruments. Please don't hesitate to contact me if you have any questions.

Sincerely,

/s/

Tara Federici
Vice President
Technology and Regulatory Affairs

Edit #	Line #	Change	Reason
1	32 - 36	Recommend inclusion of Observer Reported Outcomes (ObsROs) as a complementary Clinical Outcomes Assessment (CoA) measure to a PRO which can be obtained via observer caretakers such as family members for patients unable to report for themselves (e.g., pediatric patients and patients with cognitive disabilities).	The intent of designing a system for gathering and collecting PRO data is to ensure that the method of collection is valid and will result in reliable data to support potential clinical marketing claims for improved clinical outcomes. In specific populations where the patients are unable to report for themselves, ObsRO's provided by family members caring for patients should be considered as a complementary instrument to PRO instruments to measure treatment benefit or risk in medical device clinical trials. For this reason, we encourage the Agency to add ObsROs as a complementary CoA method to PRO and to publish guidance for the other types of CoA.
2	33	Add the following: "visual analog **and numeric rating** scale**s** (such as measures of pain severity), …"	Providing an additional example of a commonly used assessment type adds clarity and represents a broader set of assessments.
3	71	We recommend that the guidance also state that PRO instruments do not only need to be considered for clinical studies and clinical outcome measures but may also be valuable early in the design and development of the device or throughout the device lifecycle to improve device usage and safety. In these situations, valuable insights can be obtained through early simulated use testing by patients that may lead to safer products used more effectively by patients.	The guidance does discuss the use of PROs throughout the entire product life-cycle but appears only to discuss the use of PRO Instruments in the context of clinical studies and clinical outcome measures. We recommend adding this statement to ensure that the use of PRO instruments can also be used to support smaller tier claims for device usability and safety that do not necessarily need to be collected via a clinical study.
4	75 - 76	Strike and add the following: "FDA ~~determines~~ **assesses** the validity evidence ~~needed to support its specified use for a regulatory purpose~~ **based on qualitative patient input and quantitative evidence."**	It is up to the sponsor to determine the evidence needed and for FDA to assess that evidence. Clarifying that validity is determined by the qualitative and quantitative support package provides more confidence in the process.

Edit #	Line #	Change	Reason
5	77	Please clarify the reference for footnote 11.	We believe footnote 11 is the MDDT (Medical Device Development Tools) link within footnote 10, however, it is not clear.
6	126	This guidance does not mention selection decisions based on, for example, licensed vs. free use; measurement intervals and time windows per interval; online application vs. paper-based forms; and purpose classifications such as 'General health', 'Condition specific', 'Quality of life' (with utilization in QALY (quality-adjusted life-year) calculations/Health economics) and 'Satisfaction'.	Perhaps these practicalities are not the intention of this guidance but we think these are important conditions to consider in the PRO selection process.
7	128	Strike and add the following: (e.g., primary, ~~key~~ secondary, ~~or~~ exploratory **or safety**)	Secondary endpoints can be key or simply secondary endpoints. Being silent on the type of secondary endpoint may be clearer than specifying "key" secondary. The document mentions PROs for safety endpoints; however, safety was not mentioned in line 128. Adding safety to line 128 helps make statements about endpoints consistent throughout the document.
8	130	Change "its" to "the PRO instruments"	Aligns with Lines 126, 128.

Edit #	Line #	Change	Reason
9	133	Add the following: PRO instruments should be **relevant** ~~and~~ should not include items that could be misinterpreted or that are not applicable to the intended population.	For example, "use handrails on stairs", when that's common practice and not related to the condition; "get in/out bath" when a large proportion of the population only has a shower; "gardening" when the population lives mainly in apartments or in homes without a garden. Instead, these items should be replaced by other activities that are less specific and more general.
10	143	Recommend adding the following: **Another consideration is the applicability of a PRO instrument for one patient population to another without going through a formal cognitive debriefing and validation exercise. For example, a PRO instrument developed for patients to report pain associated with insertion of IV catheters across all ages can be an acceptable PRO instrument for recording pain scores in patients using wearable drug delivery devices with a pump and needle insertion. In this instance, the same PRO instrument may be applicable because of its broad applicability, study objectives, and context of use. Justification for the selection will still need to be documented.**	The following text addition is recommended because the PRO compendium referenced in the guidance mentions using the EQ5D for an implantable hemodynamic device. However, the EQ5D was tested in a variety of patients and is a general Quality of Life (QoL) instrument. Similarly, the use of the Beck Depression Inventory (Depression PRO) for the Maestro Rechargeable Solution, which is a neuromodulator for obesity could have broad applicability. However, the guidance at present does not provide examples for how or when it might be acceptable to use a broadly designed PRO Instrument in various patient populations where they might be of benefit. Right now, the draft guidance appears to be more restrictive and burdensome, suggesting that each time a modification is made one needs to establish validity of the adaptation, which will be costly, time-consuming and burdensome. As such, we provide the suggested text to serve as an example of how one might apply an existing tool for one type of patient population to another.

Edit #	Line #	Change	Reason
11	235	Strike and add the following: ~~Sponsors often choose to select from existing PRO instruments rather than develop a new PRO instrument.~~ **When selecting PRO instruments, Sponsors may consider selecting from existing PRO instruments, as this will allow comparisons of study outcomes as well as determining the effectiveness of study treatment by referencing the MCID of that particular PRO instrument. When existing PROMs are not feasible, a new PRO instrument may be developed, however the Sponsor should be aware of the cons of introducing more heterogeneity in outcome metrics (Lan, 2020 [https://www.arthroplastyjournal.org/article/S0883-5403(20)30680-X/fulltext]).** Existing PRO instruments can be used as-is, modified, or adapted, which is often less resource intensive than creating a new PRO instrument due to the ability to leverage existing validity evidence. Modifying or adapting an existing PRO instrument may be a least burdensome approach for a new COU. FDA could see the possible benefit of the modification or adaptation of existing PRO instruments where it is feasible and such an approach would still result in a relevant and reliable PRO instrument for the COU.	Within the orthopedic field, there is already too much heterogeneity in outcome metrics, hindering comparison of data among studies or determining relevant MCIDs (minimal clinically important differences). Ref - https://doi.org/10.1016/j.arth.2020.06.036
12	166	Add the following: Concept elicitation interviews identify or confirm the concept(s) measured by the PRO instrument as well as what aspects of the concept are most important to the patients, such as the frequency, severity, and/or interference with daily life, **treatment burden, or other quality of life measures (e.g., ease-of-use).**	Helps to clarify that concepts of interest can go beyond symptoms (e.g., treatment burden).
13	188 - 189	We recommend the addition of a footnote for the Patient Science and Engagement Program similar to what was done for the "Voluntary Q-submission program".	A reference to information on the Patient Science and Engagement Program would be helpful.

Edit #	Line #	Change	Reason
14	201 – 203	Revise as follows: **The sponsor** ~~FDA~~ determines the strength of evidence needed to support the measurement properties of a PRO instrument **along with the rationale for the level of evidence** based on the role of the instrument specified in the clinical study protocol and statistical analysis plan. **FDA provides direction and input on the proposed strength of the evidence.**	Based on the particular product, the role of the PRO in the clinical study and whether it is an already validated PRO or new PRO, it is up to the sponsor to propose the level of evidence and accompanying rationale and for FDA to respond.
15	216 - 219	Strike the following: The sponsor should plainly state and clearly identify the PRO instrument's COU in the clinical study protocol and statistical analysis plan (e.g., pain intensity as the concept, reduction in pain intensity as the primary effectiveness outcome with the endpoint being a ~~30%~~ reduction in the pain intensity scale score at three months compared to baseline).	Although the language of the guidance is intended as an example, we recommend using more general language. For example, what if analysis pointed to a 28% improvement which does not meet the 30% threshold? That is still a reduction but does not meet the set criteria so the endpoint would not have been met. Small companies may be misdirected by the example and assume that all endpoints must meet a percentage reduction.
16	220	Add the following: ...compared to baseline. **If baseline (i.e., pre-procedure) assessments are not meaningful (e.g., patients have no level of an attribute being measured), assessing differences of the PRO at endpoint rather than change from baseline is appropriate.**	When assessing outcomes with a device having a baseline (e.g., pre-procedure), assessment is not always meaningful or appropriate. For example, a procedure to restore vision or add a prosthetic would result in a change from no value (or no meaningful value) at baseline to follow-up. In these cases, assessing differences of the PRO at endpoint rather than change from baseline is appropriate. Asking patients to complete baseline (pre-procedure) assessments when they have no meaningful level of the attribute being assessed increases patient and trial burden and introduces potential measurement error. The importance of assessing the difference at endpoint when a change from

Edit #	Line #	Change	Reason
			baseline analysis would not result in useful information occurs more frequently in device vs. pharmaceutical submissions and a more detailed section or entire paragraph on this may improve the guidance.
17	222 - 223	Consider making this language more inclusive of engagement throughout the TPLC (Total-Product-Life-Cycle), not just the study design stage prior to IDE (Investigational Device Exemption) submission.	The guidance is quite focused on the use of PROs in pre-market studies and submissions for initial approvals. However, additional guidance, thinking, or examples of how PROs could be used in post-market studies would be helpful.
18	233	Recommend adding specific examples to this section that include modifications to PRO Instruments that FDA considers to be acceptable without the need to revalidate the entire PRO instrument. For example: The SF36 was used to support labeling claims for an implantable Artificial Disc – a device used for reconstruction of the spinal discs. The SF36 is a general QoL PRO to assess items such as "pep/life, energy, feeling of accomplishment, mental health, social impact," etc. Such concepts do not have direct context of use with the device but can be modified and applied to support collection of PRO data to support future claims.	The guidance states that companies may need to modify or adjust PRO Instruments to make it more appropriate for their cohort but it does not provide any examples of the types of modifications that would or would not require revalidation of the PRO Instrument. This is deficient because typically modifications are not allowed to be made to a PRO instrument without revalidation and validating a PRO is very timely, costly and burdensome. As such we recommend that the FDA provide additional examples of modifications that may be appropriate to implement to an existing PRO instrument without extensive re-validation of the entire PRO so that sponsors can proceed accordingly. This information will also be helpful when approaching the Agency with proposed PRO instrument modifications to review when validation is or is not needed.

Edit #	Line #	Change	Reason
19	242	Add the following: **When modifications are made, this should be clearly described in the documentation and any following publications to allow proper comparisons among study data**.	To allow valid comparisons of study data.
20	247	Add the following: **Also consider the option of crosswalks with other PRO measures for additional evidence.**	To allow additional comparisons.
21	258	Add the following: Real-world evidence derived from multiple sources outside of the clinical research setting (such as electronic health records, **peer-reviewed publications,** claims and billing activities, product and disease registries, or health-monitoring devices) may be used to generate validity evidence for PRO instruments.	RWE can take on many forms and as such, we recommend identifying specific types of RWE that can be used for PRO instrument development. In this case, we have recommended specifically identifying peer-reviewed publications as one example, because they can often serve as a source of RWE for new evaluation methods and can point to other potential applications of such methods and the data is generally accepted by the medical and scientific community.
22	262	With the proliferation of real-world data (RWD), it is possible that PRO instrument development could be nested in a RWD source. **For example, ….**	The recommended change is the insertion of an example from an instance where the Agency accepted an COI/PRO that was validated RWD evidence. Throughout the document the Agency has made references to examples of concepts to further the understanding of the reader. See lines 216-220 (pain use) and lines 180-184 (itch).

Edit #	Line #	Change	Reason
23	270	Add the following: Sponsors proactively developing or modifying PRO instruments for use in future product development may want to also consider using early feasibility, phased clinical studies, **real-world representative samples**, pivotal clinical studies, and/or post-approval studies to generate quantitative validity evidence.	Add real-world representative samples to types of data that can support the quantitative assessment of PROs. Real-world data collection can help establish population norms and may allow for the collection of a relatively larger sample for quantitative analysis which may be difficult to obtain in small trials and in rare conditions.
24	277	Recommend clarifying the statement around use of the PRO to support specific statements regarding safety and/or effectiveness.	Why spend time and effort on a study if the information cannot be used to support products and make new claims?
25	341	Strike the following: A type of ~~clinical~~ outcome assessment that is based on a report that comes directly from the patient about the status of a patient's health condition without interpretation of the patient's response by a clinician or anyone else.	Patient reported outcomes may not always be clinical outcomes. For example, patient's comfort when being treated/using the device, and/or patient's confidence in their ability to use/operate the device, etc.