August 9th, 2021

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

Re: Docket No. FDA-2020-D-2303: Core Patient-Reported Outcomes in Cancer Clinical Trials

Dear Sir/Madam:

The Biotechnology Innovation Organization (BIO) thanks the Food and Drug Administration (FDA or Agency) for the opportunity to submit comments on the Draft Guidance: *Core Patient-Reported Outcomes in Cancer Clinical Trials* (Draft Guidance).

BIO is the world's largest trade association representing biotechnology companies, academic institutions, state biotechnology centers and related organizations across the United States and in more than 30 other nations. BIO's members develop medical products and technologies to treat patients afflicted with serious diseases, to delay the onset of these diseases, or to prevent them in the first place.

BIO applauds the Agency on the release of this Draft Guidance and believes it is a good step towards providing Sponsors with greater clarity around expectations on utilizing core patient-reported outcomes (PROs). The identified core PROs and considerations and recommendations within the Guidance seem reasonable with appropriate flexibility to ensure the PROs and tools utilized to gather the data are fit-for-purpose and most relevant to the patient population, biopharmaceutical development, and goals of the clinical trial. While we acknowledge that this Draft Guidance is specific to PROs for cancer clinical trials many of the concepts can and should be utilized more broadly and we encourage the Agency to release additional guidance on broad use and applicability of various types of patient experience data (PED), including PROs. We also encourage the Agency to solicit feedback from the patient community regarding patient-focused drug development (PFDD) related guidances. Their viewpoints on these guidances will be critical as we move from developing medicines for patients to developing medicines *with* patients.

We appreciate that the Draft Guidance recognizes that a core PRO set can be helpful and provide a "minimum expectation for patient experience data" but "may not include all important patient experience outcomes to measure in specific disease contents" (lines 66-68). This is an important point to ensure that the Sponsor is able to customize the PED utilized for a specific patient population and trial and as new and innovative ways to collect PED and types of PED become available, these are able to be utilized.

Early consultation and discussion between FDA and Sponsors regarding the use of PROs and associated topics (e.g., instrument, trial design, labeling) continues to be important and we are glad to see this continued recommendation in the Draft Guidance. However, we note that there is currently little concrete guidance from FDA regarding topics such as timing,

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meeting type, who should be included in the meetings, and the type of data and necessary information. Also, there is little guidance on the possibility of any parallel advice with other Health Authorities. It would be beneficial to all Sponsors, and the Agency, if additional guidance on these and other important interaction aspects were given.

BIO believes that it is critical that the core PROs and other PED utilized in the development of a biopharmaceutical product balances the information gleaned and the burden on patients. The proposed core PROs include disease-related symptoms and symptomatic adverse events. BIO notes that these concepts and questions may be very similar and may appear to be repetitive and burdensome to patients. Additional guidance from FDA on how to balance collecting the appropriate data while not overburdening patients would be helpful.

Further, instead of adding role function to the core concept, from a clinical perspective, we recommend being more flexible so that the functional scale(s) based on the context of a given disease can be chosen. Alternatively, a holistic approach including all concepts could be an option. Quality of Life (QoL) is multi-dimensional and could be more meaningful to understand what is most important to patients with a certain condition. For example, patients with bone or soft tissue sarcoma after amputation found role and social function as well as body image more impactful on their QoL than physical function, while good physical function and a normal gait seemed to be most meaningful for patients after limb preserving surgery. Additionally, we suggest adding treatment symptoms to the list of core PROs to avoid measurement redundancy across disease symptoms and treatment symptoms.

With the COVID-19 public health emergency, utilization of decentralized clinical trials, or hybrid approaches, have gained traction and we anticipate this trend will continue even after its resolution. Additional guidance regarding the use of PROs in trials outside of the clinic would be helpful. For example, guidance covering (1) the acceptable timeframe for completing PROs outside the clinic (e.g., within 24 hours of the scheduled clinic visit, 24 hours before the clinic visit but not after) and (2) whether mixed administration (patients choose whether to complete at the clinic or at home) would be permissible to allow for greater flexibility and choice for patients.

It would be helpful for the FDA to address the topic of PRO data collection and adverse event (AE) reporting in clinical trials and clarify how PRO data complement safety data. Our understanding from various public forums with the FDA Oncology Center of Excellence (OCE) is there is no regulatory requirement for PRO data be reviewed or reconciled with safety data. Further, there was acknowledgement of a clear distinction between these two sources of data and while complementary, are expected to differ and may not correlate. It was also discussed in these forums, that PROs should not inform gaps or errors in safety measurement. We suggest that FDA clarify that there is no regulatory requirement for PRO data to be reviewed to identify safety events at the subject-level or population-level during or at completion of the clinical trial.

While we appreciate the detailed assessment frequency in Figure 1, we note that it is quite complex and could present significant operational challenges if a Sponsor attempted to deploy a non-ePRO for such an assessment frequency, and in some circumstances, (e.g., infrastructure or device literacy challenges) the ePRO may not be the preferred mechanism.

Therefore, additional guidance from the Agency would be helpful to understand how to balance the complexity of the assessment with potential operational challenges or patient preferences.

The Draft Guidance includes a section on labeling considerations but does not specify how the FDA will use the core PRO set for regulatory decision-making beyond a general statement for benefit/risk assessment. The goal of PFDD is to ensure that the patient perspective is captured and meaningfully incorporated into drug development and evaluation. Moreover, clinical trials of oncology products receiving breakthrough designations and accelerated pathways may have limitations in study design and conduct of the trial that would make it challenging to receive a label claim for the PRO evidence. It would be helpful for FDA to re-iterate the goals of PFDD and how the core PRO set will inform regulatory decision-making beyond obtaining a label claim in the Final Guidance. In addition, we encourage the FDA to continue to explore pathways to effectively communicate PRO evidence to patients, caregivers, and other lay persons via Project Patient Voice and other initiatives led by FDA, Sponsors, and other stakeholders.

We encourage FDA to continue collaborations and inclusive discussions regarding PED as these concepts maybe relevant to other stakeholders and decision-makers. Ensuring that PED is holistic and fit for multiple purposes and stakeholder use will be important.

Finally, we suggest that this Guidance include more pediatric–specific guidance as, pediatric cancer, especially in hematological cancers are on the rise. Similarly for rare-disease cancers such as HCC/ ESCC, WM, APL and other rare neoplasmic conditions. The same standards for effect sizes and/or patient reported understanding of the treatment versus disease impact might not apply (e.g., in HCC patients suffering from multiple comorbidities such as hepatitis and liver cirrhosis along with the cancer).

BIO appreciates this opportunity to comment on the Draft Guidance: *Core Patient-Reported Outcomes in Cancer Clinical Trials*. Specific comments are included in the following chart. We would be pleased to provide further input or clarification of our comments, as needed.

Sincerely,

/S/
Victoria A. Dohnal, RAC
Director, Science and Regulatory Affairs
Biotechnology Innovation Organization

SPECIFIC COMMENTS:

SECTION	ISSUE	PROPOSED CHANGE
I. INTRODUCTION		
Lines 23-26:	The Draft Guidance states "Guidance specific to PRO endpoints and details of analytic methods are not comprehensively covered. FDA does not endorse any specific PRO measure and examples within this document are illustrative and should not be construed as endorsements." The Guidance references the May 2021 Pediatric Subcommittee of the ODAC Meeting wherein the recently developed Pediatric PRO-CTCAE (Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events) was discussed.	Please reference published sources (e.g., Reid et.al) regarding the selection of the most appropriate items for PRO-CTCAE.
Lines 35-36:	The Draft Guidance states "PRO measurement may not be feasible in all cancer trial populations (e.g., in patients with significant cognitive impairment)." This sentence implies that the experience of patients with cognitive impairment cannot be captured. However, observer-reported outcomes (ObsROs) from a caregiver may be an option.	We suggest the text be edited to reflect the possibility of ObsROs being utilized. We suggest text such as the following: "PRO concepts may not be feasible to collect directly from patients in all cancer trial populations (e.g., in patients with significant cognitive impairment); however, although beyond the scope of this guidance, observer-reported outcomes (ObsROs) from a caregiver may be an option." Also, clarification is needed as to whether this Draft Guidance applies to pediatric populations (as parents or caregivers may have to be involved) or refer to applicable guidance/initiatives (Pediatric PRO-CTCAE) if not.

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		Finally, clarification regarding the timing of introduction of PRO assessments in drug development would be helpful.
II. BACKGROUND		
Lines 60-61:	The Draft Guidance states "PRO measures can facilitate high quality data on patient-reported symptoms and functional impacts." Selecting fit-for-purpose PRO measures may not guarantee "high-quality data" (which can be a subjective characterization of data) because there could be issues such as missing data.	BIO suggests editing the text to read: "PRO measures can facilitate ~~high-quality data on patient-reported symptoms and functional impacts~~ collection of reliable and relevant data for the target population".
Line 63-68:	The Draft Guidance states "A core set of PROs including disease symptoms, symptomatic adverse events, and physical function, that may be important contributors to a patient's health-related quality of life (HRQOL) and that may be sensitive to the effect of the disease and treatment under study has been described. This guidance expands on this concept, acknowledging that a core PRO set can provide a minimum expectation for patient experience data across cancer settings, but may not include all important patient experience outcomes to measure in specific disease contexts." Insights attained through R&D Patient Engagement and 2-way dialogue with patients and the patient community can generate valuable information to inform PRO strategy and suggest revision or expansion of PROs beyond the minimum expectation core PROs.	It would be helpful for the Guidance to discuss ways in which qualitative patient experience data (PED) obtained via patient engagement activities such as advisory boards, clinical trial simulations etc. can be communicated to the FDA to impact decision making. As noted in our general comments, topics may include what patient experience data and when; in what venues, forums and meetings can this be communicated to FDA; during what conversations and at what decision points; and what subject matter experts are most appropriate to attend such conversations.

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III. CORE PATIENT-REPORTED OUTCOMES		
Line 80:	BIO notes that "role function" was previously considered too distal; it is important to understand the rationale why this is included in the core set. It would be helpful to have further background on rationale to include "role function" which goes beyond the cited "Ref. 6" in the Draft Guidance.	Please add or reference the rationale for adding Role Function as a core patient reported outcome.
Line 82-88:	The Draft Guidance states "Additional PROs that are important to patients, outside of the core concepts in this section, could be prospectively specified and collected in clinical studies based on the context of a given clinical trial. For instance, swallowing function and cognitive function may be outcomes of interest in addition to the core set in the context of advanced esophageal cancer and neuro-oncology, respectively. Selection of outcomes outside of the core PRO set should be carefully considered to minimize patient burden and improve the quality of data collected by focusing on the most meaningful and measurable outcomes." Patient insights attained through R&D Patient Engagement and 2-way dialogue with patients and the patient community can generate information around the patient burden and how this burden is weighed in the context of the value of the additional measures.	Similar to our comments in lines 63-68, we request the Agency specify the ways in which qualitative patient experience data (PED) obtained via patient engagement activities such as advisory boards, clinical trial simulations etc. can be communicated to the FDA to impact decision making.
Line 84-85:	The Draft Guidance states "For instance, swallowing function and cognitive function may be outcomes of	We suggest editing the text to read:

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	interest in addition to the core set in the context of advanced esophageal cancer and neurooncology, respectively." We suggest editing the text to better articulate a variety of important factors. If patients have to take multiple tablets, the taste and ability to hold down medication may be a factor in the patient experience.	"For instance, ~~swallowing function,~~ acceptability (taste, ability to swallow, and/or ability to hold down he medication), and cognitive function…"
Line 88:	We suggest that the Guidance address the use of patient preference studies and how these studies relate to the core set.	We suggest adding the statement: "Sponsors conducting patient preference studies to support registration of anti-cancer therapies should consider including these core outcomes as attributes in the preference study so that the resulting preference data will be consistent with outcome data collected in clinical studies."
IV. CONSIDERATIONS FOR INSTRUMENT SELECTION TO MEASURE THE CORE PATIENT-REPORTED OUTCOMES		
Line 117:	We suggest including an additional consideration for instrument selection.	We propose adding the following to this section of the Draft Guidance: "PRO instruments selected may not be representative of the complete patient experience, particularly if the results of these items are not consistent with the results of the other domains. PRO measurement strategy should focus on assessment of core disease and treatment symptoms and its associated impacts (e.g., physical function)"
Lines 124-126:	The Draft Guidance states "For instance, a well defined physical function scale should include questions on a range of activities requiring physical	BIO recommends clarifying how this may apply to PROs such as the MDASI which asks about how

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	effort and should not contain specific questions tied to or dependent on other concepts such as side effects or symptoms."	patients' symptoms have interfered with their lives and how they feel and function. Further, we note that this recommendation seems challenging as the level of physical functioning depends on symptom burdens from the disease and treatment. As such, we suggest **removing** the following from the text: "and should not contain specific questions tied to or dependent on other concepts such as side effects or symptoms."
Line 126:	We suggest the addition of another consideration for instrument selection.	We suggest adding the following: "Consider identifying the optimum number of specific patient-reported concepts to measure and avoid duplication where feasible to reduce respondent burden and maximize the quality and completeness of PRO data".
Lines 128, 180, 187, 214:	In these sections, the Draft Guidance states "In some cases, subscales or subsets of questions from existing PRO instruments may be used to inform the benefit/risk assessment and support labeling claims if prospectively defined and their measurement properties have been adequately evaluated.	EORTC-QLQ-C30 has historically been used in oncology clinical trials as the full 30-item instrument. The examples for physical function and role function seem to indicate that these domain sub-scores can be administered separately, without having to administer the entire C30 during all visits, if measurement properties have been properly evaluated. Taken together, these sections seem to indicate that, within a single clinical trial, the full C30 can be administered during select visits (to satisfy

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	Physical Function: Sponsors should select scales that measure defined concepts and assess varying levels of ability to perform activities that require physical effort. Role function: The impact of a treatment on the ability to work and carry out daily activities is important to patients and may also provide some information on other functional abilities such as cognitive function. When using a modular approach where these elements are able to be assessed and analyzed separately, different assessment frequencies can be selected that can reduce the response burden to patients."	other stakeholders), yet only sub-scores (e.g., physical function) can be administered during other study visits (thus reducing overall number of items patients complete for a given study). Further clarification on this point would be helpful.
Line 130-134:	The Draft Guidance states "Early consultation with FDA is recommended regarding selection of appropriate instrument(s) for a particular cancer clinical trial context. Ideally, interactions with the agency would include discussion of the PRO instrument, trial design, and labeling considerations."	As noted in our general comments, it would be helpful for the Guidance to discuss the meeting type (and timing) that would be most appropriate whether outside participants (patients, advocates, etc.) would be allowed to participate or provide input.
Line 148-149:	The Draft Guidance states "Alternatively, a frequency scale for one or more of these items may also be considered (e.g., ranging from none of the time to all of the time).	We suggest the inclusion of examples or considerations when assessing the dimensionalities of a symptom (e.g., evaluating severity of pain, assessing the frequency of vomiting).
Lines 154-158:	The Draft Guidance states, "For example, if neuropathy is expected on active control only, an item assessing neuropathy should be included in both the active and control arms. FDA considers the	BIO suggests FDA use an alternative example that is also clear to the patients. For example, Treatment Satisfaction Questionnaire for Medication could be used. TSQM has been used longer and has shown its

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	National Cancer Institute's PRO version of the common terminology criteria for adverse events (PRO-CTCAE) to be an example of one acceptable item library for assessment of symptomatic adverse events"	sensitivity and reliability in different drugs, additionally there are different & shorter version of it available (e.g., 9-item version) and that it will put less burden on the patients than the PRO-CTCAE. TSQM has been translated in 112 languages, available in paper & e versions, with time to completion of less than 5 min, recall period of 2-3 weeks (in accordance with FDA recall guidance). Domain covered are: Side effects (5 items) – α=0.88 Effectiveness (3 items) - α=0.88 Convenience (3 items) - α=0.90 Global satisfaction (3 items) - α=0.86 Additionally, there is no weighting in scoring which makes the analysis less complicated. The concept elicitation and Item generation (psychometric validity) meets all of the 4 major FDA/EMA requirements: 1) lit review (G2), 2) instrument review (G2), 3) focus group (G4), and 4) in-dept interviews with patients (G4). Ref: Atkinson MJ, Sinha A, Hass SL. Validation of a general measure of treatment satisfaction, the Treatment Satisfaction Questionnaire for Medication (TSQM), using a national panel study of chronic disease. Health Qual Life Outcomes. 2004 Feb 26;2(1):12
Line 168-178:	If the Draft Guidance finds the use of overall adverse events acceptable, then the Agency should consider utilizing a global impression of health state or QoL in the same manner. A global impression measure is	We suggest adding the use of a global impression measure and QoL.

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	informative and widely used in the real world by other Health Authorities such as EMA, HTA agencies.	
Lines 174-177:	The Draft Guidance states "For example, "Please choose the response below that best describes the severity of your **overall side effects from treatment** over the past week" (where 0 represents none and 3 represents severe). Examples of existing single item global side effect bother questions include the GP5 question from the Functional Assessment of Chronic Illness Therapy (FACIT) item library, and the Q168 question from the European Organisation for Research and Treatment of Cancer (EORTC) item library." Different side effects may differ in their importance to different patients. If patients cannot assess which side effects are more or less severe, how can patients make well-informed treatment choices? Side effects may be severe, but this may not correlate to patients' unwillingness to undergo treatment given the importance of the treatment they receive.	We suggest FDA consider framing symptoms in the context of "bother" or "importance" rather than overall side effects.
Lines 181-185:	The Draft Guidance states "One option to consider is the Patient-Reported Outcomes Measurement Information System (PROMIS)® physical function item bank. Another commonly used physical function scale that can be considered is the EORTC Quality of Life of Cancer Patients QLQ-C30 physical function scale."	We recommend clarifying whether these general measures need to be assessed for the specific context of use.

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Lines 187-190:	The Draft Guidance states "The impact of a treatment on the ability to work and carry out daily activities is important to patients and may also provide some information on other functional abilities such as cognitive function."	The concept of cognitive function may be worthwhile as its own measurement concept outside of the role function umbrella and suggest updating the Guidance.
Lines 193-195:	The Draft Guidance states "For instance, using PRO measures to support a claim of equivalence or non-inferiority between two arms is problematic without sufficient support that the sensitivity of the measure is adequate."	We recommend that FDA provide clarity on the type of sensitivity analysis (e.g., conducting sensitivity to change analysis is adequate).
V. TRIAL DESIGN CONSIDERATIONS		
A. Assessment Frequency		
Line 210:	We suggest additional bullets regarding what should be considered when determining the frequency of PRO assessment for core PROs.	We suggest adding the following two bullets: • Optimize the frequency and timing of assessments • Prospectively put in place procedures for minimizing missing data, including obtaining PRO data from patients at time of early withdrawal, and include these procedures in the protocol. We also request that FDA include additional guidance on the factors they would consider when assessing whether the frequency of assessments is optimal.
Lines 217-219:	The Draft Guidance states "An example of a PRO assessment strategy that assesses PRO more frequently in the first 8 weeks of treatment would be suitable across most drug administration schedules and is provided below"	We suggest editing the text to read: "An example of a PRO assessment strategy that assesses PRO more frequently in the first 8 weeks of treatment would be suitable across most drug

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	In the example, more frequent PRO assessments are proposed for the first 8 weeks. But the time to onset of symptomatic AEs may vary by treatments. Since this Guidance seems to inform Phase 3 trials, when the safety profile is usually well understood, we recommend aligning assessment frequency with the safety profile of the product under investigation.	administration schedules and is provided below. Note that the time of onset of symptomatic AEs may vary by treatments. Since the safety profile is usually well understood, align assessment frequency with the safety profile of the product under investigation"
Line 221, Figure 1:	This table implies that different domains could be administered independently and using a different administration schedule. For established instruments, like EORTC QLQ-C30 or FACT-G, is the Agency suggesting that individual domains/ instruments be administered at certain timepoints (instead of the entire instrument) within the overall administration schedule? Is there a requirement from the instrument developers that these established PROs be administered together, or in a more collected/ holistic fashion? And is there a risk that selecting and administering only select domains, that this could be viewed as a scoring deviation and impact the interpretability of the data?	Further guidance and clarity is requested.
Line 255-257:	The Draft Guidance states "Carefully record the use (including changes in dose) of concomitant medications or therapies that may affect the interpretation of the concept(s) being measured (e.g., use of concomitant pain medications when measuring pain)." Companies are beginning to propose the use of PROs as early as phase 1b to help inform the key	Since PROs are being explored in early drug development to inform key concepts it would be helpful for the Guidance to discuss implementing PROs in early development.

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	concepts/items that have potential to change with treatment to subsequently inform PRO strategies for key pivotal trials.	
Lines 229-231:	The Draft Guidance states "In the case where both arms have orally administered treatments on a daily schedule, assessments could be less frequent given the lack of cyclic variability surrounding administration schedules seen with IV chemotherapies."	We recommend including guidance about trials where the treatment arms have different administration schedules and/or different AE profiles/onsets, including the timing of onset.
Lines 233-258:	In addition to the bullets in this section, we suggest adding frequent data transfers/data review in protocol or monitoring plan as part of other trial considerations.	We suggest adding the following text: • Frequent data transfers and data review should be documented in protocol or monitoring plan to help identify missing or incomplete data early
Line 246-247:	That Draft Guidance lists "Reasons for missing PRO data should be documented and included in the analysis dataset." as an item to be considered to mitigate missing data.	Currently, most of the ePRO vendors do not have ability to provide patient ability to report missed data in the system directly or reasons for missing diary. Typically, PRO would not be completed because of the following reasons: 1. Patient forgot or could not complete diary 2. Device or network issues Normally, device or network issues can be identified through helpdesk tickets if reported. Patients that do not enter information for other reasons are not captured. However, currently merging technical issue and specific diary is not easy as this information is captured in different vendor systems.

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Line 258:	Patients' knowledge of treatment assignment may lead to systematic overestimation or underestimation of the treatment effect, the magnitude of which is currently unknown. We suggest adding a consideration on how this can be addressed.	We suggest adding the following bullets: • When blinding is not feasible, or there is high likelihood of inadvertent unblinding due to toxicity, lack of blinding could be overcome by demonstrating a large and durable magnitude of effect in the setting of strict adherence to a carefully conducted clinical trial. • PRO results can be further supported by findings from other endpoints and by sensitivity or subgroup analyses comparing the findings relative to other data collected in the trial.
B. Other Trial Design Considerations		
Lines 249-250:	The Draft Guidance states "Provide a pre-specified plan for the analysis of PRO data including the threshold for and interpretation of a meaningful change in score(s), if relevant."	We recommend that FDA specify the type of meaningful change (i.e., MWPC) as well as clarify when MCT would not be relevant.
VI. LABELING CONSIDERATIONS		
Line 262-264:	The Draft Guidance states "Inclusion of PRO data in the product label will depend on the adequacy of the design and conduct of the trial, the strengths and limitations of the instrument within the given context of use, and the quality of submitted data."	There is very little detail on endpoint definition or analysis (for example nothing on PRO estimands in oncology), it would be helpful if additional detail on these topics be expanded where included in the Guidance.
Line 266:	The Draft Guidance states "Lack of statistical superiority is not suitable evidence for claims of "no meaningful difference.""	It would be helpful for the Guidance to include information on how to report as well as include results that do not have a formal analysis pre-specified or reference the appropriate Guidance.

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Lines 267-270:	The Draft Guidance states "" A claim of non-inferiority or equivalence should be supported by evidence that the sensitivity of the measure is adequate and the trial should be adequately designed, including justification for the selected non-inferiority margin, to make such a claim as documented in the statistical analysis plan."	Additional guidance would be helpful on criteria to justify the non-inferiority margin.
Lines 281-282:	Regarding exploratory PRO finding, the Draft Guidance states "FDA will review these data and will evaluate and consider whether inclusion of descriptive PRO data in labeling is appropriate on a case-by-case basis"	Additional clarity regarding how FDA will determine when PRO data are "appropriate" for inclusion as descriptive data. Specific examples where PRO data were included as descriptive information in the clinical studies section of labeling would be helpful.