December 14, 2018

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

Re: Docket No. FDA–2018-N-2455: FDA's open docket entitled "Patient-Focused Drug Development Guidance: Methods to Identify What Is Important to Patients and Select, Develop, or Modify Fit-for-Purpose Clinical Outcome Assessments".

Dear Sir/Madam:

The Biotechnology Innovation Organization (BIO) thanks the Food and Drug Administration (FDA) for the opportunity to submit comments following the public meeting on Patient-Focused Drug Development (PFDD) Guidance: Methods To Identify What Is Important to Patients and Select, Develop, or Modify Fit-for-Purpose Clinical Outcome Assessments.

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 members develop medical products and technologies to treat people afflicted with serious diseases, to delay the onset of these diseases, or to prevent them in the first place.

BIO commends the FDA for the tremendous work that the Agency has done in order to better ensure that patient experiences are more systematically collected and used to inform the development and review of new therapies. BIO particularly appreciates the Agency's work to develop guidance documents and discussion guides prior to public meetings. It is through public discussion and the development of guidance documents and the collaboration of all stakeholders, including industry Sponsors, FDA reviewers, and patients and patient organizations, that will allow for patient experience data to be collected and used more widely in drug development and review.

BIO strongly believes that in order to truly support patient-focused drug development, patient experience data should be considered for use throughout the drug development and review lifecycle. Appropriate fit-for-purpose tools for collecting patient experience data have the potential to inform protocol design, endpoint development, benefit-risk assessments, and labeling, among other aspects of drug development and assessment. To encourage stakeholders to collect fit-for-purpose patient experience data, we request that the FDA more clearly indicate the breadth of regulatory decisions for which they will consider different types of patient experience data. To this end, BIO suggests that the Agency consider including in guidance documents or on the FDA website, External Resources or Information Related to Patient Experiences, in the form of a chart, the different drug development (e.g., internal decisions such as clinical trial design, and for which data to may not be submitted to the FDA) and regulatory decisions (e.g., benefit risk) that the FDA believes can be informed by patient experience data. This chart could be accompanied by case examples highlighting types of patient experience data and how the data was used to inform different decisions in the drug development and review lifecycle. To support these

1201 Maryland Avenue SW
Suite 900
Washington DC 20024
202.962.9200 P
202.488.6306 F
bio.org

efforts, BIO developed, a chart (see page 38 of this letter) that the FDA may consider adopting or adapting for this purpose as well as case examples (see pages 39-43). While some case examples are included in this letter, BIO will continue to collect and develop additional case study examples to share with the FDA at a future date to help inform collection and utilization of patient experience data by all stakeholders.

While BIO also agrees that FDA's upcoming PFDD guidance should be complementary to the Patient Reported Outcomes (PRO) Guidance[1], we believe that the latter is too restrictive and has as a result, limited the development and use of PRO tools/instruments to inform product labeling. In light of implementation challenges that make the PRO guidance more restrictive and to maximize utility of new PFDD guidance documents, BIO requests that FDA keep the scope broadly applicable and policy flexible. For example, the Discussion Guides refer to instrument changes that 'may alter the way respondents respond to the same set of items', including changing the timing of or procedures for instrument administration in a clinic visit, changing the application to a different setting, population or condition, changing the order of items, item wording, response options or recall period or adding to or deleting portions of an instrument, changing the instructions or placement of instructions and changing an instrument from paper to electronic format. Similar statements were included in the 2009 PRO Guidance and, and as a result made it very difficult for Sponsors to develop, validate, or repurpose existing Clinical Outcome Assessments (COAs). Given that successful repurposing of existing measures is part of the rationale for the new guidances, extra care should be taken in wording so as to avoid overly rigid interpretation.

In addition to the general comments above, we have also included the following specific responses to the questions posed by the FDA in the open docket as well as specific line edits to the Discussion Documents in tabular form.

I. PFDD Guidance 2 Discussion Document: Methods to Identify What is Important to Patients

A. Specific Questions Posed by the FDA

1) Identify best practices (qualitative and quantitative methods) for eliciting information about what aspects of symptoms, impacts of disease, and other issues important to patients that are representative of the target population of patients and caregivers. What level of detail of the methodology do you think is appropriate for this guidance?

BIO believes that the Agency should provide guidance on the range of different methods for eliciting information from patients on symptoms and impacts of disease and for a given regulatory submission. This is particularly important given that we are still in the early stages of learning how to best collect, analyze, and use patient experience data. Flexibility in the approaches that the Agency will consider is particularly important when considering

[1] FDA Guidance for Industry. Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims (2009).

the use of novel methods for collecting, extracting, or analyzing data to establish what is important to patients (e.g., social media or online focus groups as a source of patient experience data, natural language processing for collecting patient experience data). However, guidance is needed as to whether such novel forms of data could form the basis of an evidence package, or whether they would be considered supportive to more traditional methods of identifying what is important to patients.

Because the FDA will likely not be able to discuss in detail or provide best practices for all possible methods that may be acceptable for eliciting information from patients, BIO encourages the Agency to reference in the guidance and/or provide links to other resources and/or best practices that can provide that additional detail for a variety of different methods (e.g., International Society for Pharmacoeconomics and Outcomes Research (ISPOR), International Society for Quality of Life Research (ISOQOL) best practice documents, and others). The Agency may also consider including such resources on the FDA website on External Resources or Information Related to Patient Experiences. Additionally, CDRH has already begun developing guidance and other resources on patient experience data. BIO requests that the FDA indicate where there is alignment across FDA Centers on thinking related to patient experience data and, to the extent possible, reference, and use existing FDA patient experience data resources.

BIO also requests that the FDA make clear in the PFDD Draft Guidance the delineation between collection of patient experience data to inform clinical trials and patient experience data collected within a clinical trial that would be intended for submission to the FDA to inform a regulatory decision. The purpose for collecting patient experience data informs the choice of methodology standards which are different for different purposes. Holding all types of patient experience data to the same standard could place an undue burden on stakeholders in terms of data management, data standards, and reporting requirements and ultimately discourage collection of patient experience data for some purposes. Therefore, we recommend that the Draft Guidance clarify the standards FDA expects for the collection of patient experience data based on its intended use.

As mentioned above, because our understanding of the collection and use of patient experience data are still evolving, BIO requests that the Agency provide clear opportunities for Sponsors and other stakeholders to meet with or engage the Agency to discuss approaches that may be used for a program (please also see response below to Discussion Guide 2, question 9).

2) What sample size will elicit sufficient information about the patient experience to assure representativeness but is feasible?

Representativeness may be enhanced through increasing sample sizes, the nature of the sampling strategy is often more important for ensuring a representative sample which might not be feasible using a single methodology.

Additionally, the FDA discusses saturation briefly in the Discussion Document; however a more comprehensive discussion of saturation would benefit all stakeholders. While further

clarification of this point would be helpful, BIO also encourages the FDA to be flexible and note overly prescriptive as to the number of participants, recognizing that the sample size will be context specific. BIO also cautions against the Agency developing overly burdensome requirements for sample size, representation, and saturation as it may discourage stakeholders from collecting and using patient experience data to inform drug development and review.

The goal of qualitative research is to gain as much feedback as possible across a wide range of demographics and disease severity, to best identify what aspects are important to patients. Similarly, the goal of quantitative research, such as surveys, is to collect responses in a population of patients who would be likely to receive product. Given this context it would be helpful for the FDA to define "target population." For example, a "target population" could include a population similar to the disease subpopulation that would be included in the pivotal trial or it could be the population with the target disease, composed of sub-populations with different attributes (e.g., severe versus mild, advanced versus early disease, patients with comorbidities versus patients without comorbidities, or those who have prior experience participating in clinical studies versus those who do not). The Draft Guidance would benefit from additional discussion regarding what the FDA considers a "target population" and the term should be added to the glossary.

Lastly, it is important to consider the perspective of rare diseases with limited patient population where traditional approach to sample size to elicit sufficient information about the patient experience to assure representativeness may not be feasible. Additional flexibility and openness to innovative approaches, as well as embracing more qualitative methods when adequate numbers of patients may not available for statistical approaches, should be addressed in the guidance.

3) What other data (e.g., data from social networks, accelerometry, room surveillance) can be used to elicit or derive information about the patient experience in a feasible manner?

BIO believes that there are numerous possible sources of data beyond traditional interviews that may be useful for collecting information from patients. In general, the guidance should signal acceptance of patient generated data. To encourage use of innovative data types and modes for collecting such data, especially those that have the ability to decrease the burden on the patient, BIO requests the Agency to provide additional information regarding how it may consider the evidentiary standards needed for such data to be used for regulatory decision-making. Statements from the Agency in guidance that such data or data collected via these modes may be considered for regulatory decision-making, if fit-for-purpose, would help encourage stakeholders to consider collecting such data. Such technologies may include those that use the passive collection of information in the home (e.g., Sensors that track movement, heart rate, sleep patterns, water retention) as well as social media, weather data, environmental assessments, work productivity, and voice data.

There is also a gap in understanding how different types of technologies fit under the broad scope of digital methods, and what regulatory standards will be required for different types of digital technologies. Additional clarification on the different types of digital technologies and the regulatory standards for each of these would be beneficial to include in guidance. Further clarification regarding how and with whom (CDRH vs. CDER) Sponsors can discuss issues pertaining to digital technologies is also important.

4) Use of social media is recognized as a potential data collection method to elicit information regarding patient experience.

- *b) Will information collected from social media sources meet the goals of Guidance 2 (e.g., collecting representative information on important symptoms, burdens, and related issues)? If yes, how do we determine the adequacy of data from social media sources?*
- *c) Is there a need for patient verification if social media is the data collection method to elicit information about the patient experience?*

BIO believes that social media data has significant strengths and limitations which are well discussed in the document. Data derived from social media can serve either to generate hypotheses or to support observations. For example, evaluation of social media/medical blogs could be used to inform a more structured and focused interview guide for one-on-one interviews. Evaluation of social media could also be used to provide further insight to findings obtained from one-on-one interviews in a larger, more representative group (as outlined in Appendix 7).

The use of data collected via social media is another area where the Agency should clearly delineate the purpose for which the data will be used, as this will inform the evidentiary standards to be met (i.e., the degree of verification needed). For example, patient experience data collected via social media to inform hypothesis generation or used in combination with other types of patient experience data may not require verification and may require different evidentiary standards compared to patient experience data collected from social media used for other purposes (i.e., to inform benefit-risk). As mentioned above, this topic and other issues regarding evidentiary standards for patient experience data may be addressed if the FDA develops a chart outlining the decisions informed by patient experience data (e.g., clinical trial design, endpoint selection, benefit-risk determinations) and the corresponding evidentiary standards required for data collected for those purposes.

In addition to the issue of evidentiary standards for regulatory use, ethical considerations and standards for the collection and analysis of social media data for regulatory consideration should also be considered. Disclosure, consent, and data ownership are key issue for consideration.

Given that all stakeholders are in the early stages of thinking about the collection of patient experience data through social media, BIO requests that the FDA consider hosting a public meeting on the topic so that all stakeholders can share thinking around the benefits,

barriers, and potential solutions for using social media to collect patient experience data. Such discussions at a public meeting may include the extent to which and under what circumstances data collected via social media will need to be verified as well as questions pertaining to representativeness of data from various digital sources (i.e., social media or other verified patient communities). Considerations for ethics approval, transparency, and informed consent in the context of use of data from social media should also be addressed. To the extent possible, BIO would be pleased to provide assistance or additional input to the Agency when planning such a meeting.

5) Important considerations are needed for special populations, such as pediatrics, the cognitively impaired, and rare diseases. What other special populations (beyond pediatric, cognitively impaired, and rare diseases) should be identified for this FDA Guidance? Are there any other factors to consider when eliciting information from special populations?

The FDA mentions special populations that may require additional considerations when it comes to collecting patient experience data. While BIO agrees with the above examples, it would also be helpful for the FDA to provide case examples containing concrete solutions and considerations as to how stakeholders may address the special populations. To this end, BIO has included case example 3 on page 43 of this letter to demonstrate considerations that can be taken into account when considering the development a PRO versus an observer reported outcome (ObsRO) for pediatric populations. Similar case examples should also be developed for the other special population categories outlined above (i.e., rare diseases and cognitively impaired) in an effort to encourage collection of patient experience data. BIO also encourages the FDA to reference in the Draft Guidance how the use of patient partners, ObsROs, or other broadly accepted tools may also be used help collect information pertaining to special patient populations.

Other sub-populations that need consideration are categories within the rare disease special population (e.g. rare pediatric, rare chronic, and rare degenerative diseases), differently abled groups such as hearing and visually impaired, or participants who may not have ready access to healthcare facilities or who may be home bound, or immuno compromised patients who require important considerations about the environment in which their experience data are collected. Pregnant women may also be considered a special population as patient experience with disease may be further impacted by pregnancy status and additional questions may need to be developed to probe or elicit patient experience information fully and accurately. The collection of information on what is important to these patients (both in terms of disease management as well as trial participation) should be carefully considered. BIO encourages the FDA to provide information to stakeholders regarding how they may address barriers faced by patients who may not easily be able to provide their input due to constraints associated with their geographical location or mobility. Such solutions may include for example, the use of telephone conferencing in lieu of in-person sessions. Information on such solutions in the guidance documents will encourage Sponsors and other stakeholders to consider collecting patient experience data even from those patients who may not easily be able to travel to a data collection site.

One of the important considerations for patients with rare diseases is that study participants may have participated in other studies. Further, the same participants who provide patient perspective or input for a clinical study design or endpoint, may then be a participant in the same study or study with the endpoint. Thus, among other factors to consider when eliciting information from the rare disease special population is the influence of trial participation on the patient's perspective. The influence of the stage of disease and available therapies should also be given consideration.

6) The level of rigor needed for generating patient experience data can vary across studies and will depend on the intended use. However, there are certain elements common to all studies such as a protocol, structured data collection, and analysis. How much detail about each aspect would be useful in guidance? On a website? Elsewhere?

BIO agrees that the evidentiary standards needed for generating and using patient experience data may vary across studies and will depend upon the intended use of the data, as well as characteristics of the patient population; however, it is unclear from the question above whether the FDA is referring to common elements for data that will be used for regulatory decision-making versus patient experience data that may inform other decisions beyond regulatory decisions (i.e., clinical trial design or other decisions made internally within a company). Additionally, further clarification is needed with respect to what is required for patient experience data with respect to labeling.

To clarify the above question as well as information included in the Discussion Document and upcoming Guidance it would be helpful for the FDA to make clear the delineation between collection of patient experience data to inform clinical studies (e.g., inform clinical design) and patient experience data meant for submission to the FDA to inform a regulatory decision (e.g., endpoint selection or benefit risk assessments). Collection for each of these uses may impact the choice of methodology used as the collection of all patient experience data may not involve the same methods and standards as are currently applicable for registrational clinical trials. Holding all types of patient experience data to the same standard could place an undue burden on stakeholders in terms of data management, data standards, and reporting requirements and discourage collection of patient experience data for some purposes.

To this end, the FDA may consider including in guidance a framework that outlines decisions that may be informed by a given set of patient experience data (e.g., product design/adaptation, clinical trial design, benefit-risk assessment, labeling, etc.) along with guidelines or guiding principles that apply to the data collected for a given decision. BIO has included a chart on page 38 of this letter that FDA may wish to adopt for this purpose. The FDA may also use case examples to demonstrate the evidentiary standards needed for patient experience data that will inform different decisions throughout the product lifecycle. For example, BIO has included cases examples beginning on page 39 of this letter. Case example 2 (page 41) includes reference to validation and determination of clinical meaningfulness when developing a new endpoint from patient experience data. This case example varies in contrast to case example 1 (page 39) where patient experience data were

used to inform elements of clinical trial design and did not require validation or determination of clinical meaningfulness. Similar examples provided in guidance would provide much needed clarity for all stakeholders regarding the FDA's thinking around the evidentiary standards for different types of patient experience data used for different purposes. BIO is working to develop additional case examples that may help provide clarity on evidentiary standards.

7) What document structure and content would be most useful for this guidance?

The information in the guidance may be more clear if the guidance was structured to distinguish methods based on the intended use (e.g., use for internal strategy versus regulatory decision-making).

8) Many potential research methods are available and not all could be included in the discussion document. Is it clear the Agency is open to discussion of the methods described and other methods, both within medical product programs and in the pre-competitive space?

BIO believes that the Discussion Document encourages Sponsors to interact early with the Agency. However, the process and proposed timings for such interactions is unclear. BIO encourages the Agency to specifically state in the guidance documents how Sponsors and other stakeholders can meet with the Agency to discuss patient experience data. We encourage FDA to engage with Sponsors and patients in patient engagement meetings or other meetings with patients—these can add great value to FDA's understanding of the patient experience. Patients sharing their experience with the FDA in such qualitative fashion in a patient engagement meeting is also a form of patient experience data being shared with the FDA. The Agency may consider including a table in such guidance that outlines the meeting opportunities for different timepoints in the drug development lifecycle whereby Sponsors and other stakeholders can meet with the Agency. We have included on page 38 of this letter a chart that the Agency may wish to adapt for this purpose.

9) What are the most important timepoints when FDA input could be maximally helpful?

BIO requests that the FDA specify in the upcoming guidance when and how industry Sponsors and other stakeholders can consult with the FDA regarding the conduct of studies and the incorporation of patients' experience into regulatory decisions. While the type and timing of a meeting that a Sponsor may need will vary over the drug development lifecycle, BIO requests that the FDA consider increasing the length of milestone meetings if Sponsors will be discussing patient experience data, providing dedicated meeting opportunities for Sponsors to discuss patient experience data (e.g., Type C meetings), providing patient engagement meeting opportunities for patients to share their experiences and perspectives with FDA, and providing opportunities for Sponsors to receive written agreement with the FDA (e.g., through a process similar to the Special Protocol Assessment). As we are still in early phases of developing best practices for rigorously collecting, analyzing, and using

patient experience data, additional opportunities to informally engage the Agency with research proposals (rather than fully-formed protocols) would foster the collection of and use of patient experience data throughout the product lifecycle. We also ask the FDA to delineate a streamlined process whereby patients and patient organizations may also meet with the FDA.

B. Additional Comments

- BIO also requests that the FDA clarify to what extent the Agency will consider patient experience data gathered solely from the United States population versus that gathered more globally in determining what is important to patients. Conversely, we also ask the FDA to clarify if data gathered from other countries could also determine what is important to patients.
- Within the Discussion Document, the FDA indicates that concept elicitation can be completed, using quantitative methods alone, rather than in conjunction with qualitative methods. Because this is a deviation from the current approach, BIO requests that the FDA provide further detail.

II. PFDD Guidance 3 Discussion Document: Select, Develop, Modify Fit-for-Purpose Clinical Outcome Assessments

A. Specific Questions Posed by the FDA

1) Does the Roadmap Diagram (Figure 3) in the Guidance 3 discussion document capture the appropriate elements to strategize for the selection and/or development of a COA for use in clinical trials? If not, what are other factors that should be considered and where should they be positioned in the diagram?

Figure 3 captures the important steps and appropriately delineates generating information to understand the disease or condition, conceptualizing treatment benefit, and selecting/developing the outcome measure. However the Figure focuses on outcomes and not experiences, specifically experiences with the experimental treatment. Experiences with treatment can only be understood from patients participating in clinical trials, but if measured using an appropriate tool could be considered as an indication of treatment benefit. For example, in Discussion Document 2, treatment convenience was discussed and is a good example of a benefit that may be perceived by patients, be a relevant component in benefit-risk assessment, and which can be measured using patient reported outcomes or interviews. BIO encourages the FDA to incorporate into guidance patient experiences and how those patient experiences can inform benefit-risk determinations.

2) Does the decision tree diagram (Figure 6) in the Guidance 3 discussion document capture the process to select, develop, or modify a COA sufficiently? If not, what are other factors that should be considered in this process and where should they be positioned in the diagram? Should this diagram replace the "Wheel and Spokes" diagram in the current PRO Guidance (Figure 3 in FDA PRO Guidance)?

BIO appreciates the FDA's inclusion of Figure 6 in Discussion Document 3 as it provides a logical flow to understand the selection, modification, or development of a COA. While BIO appreciates that the FDA has emphasized the use of existing COAs whenever possible, additional clarification from the Agency on what is considered "fit-for-purpose" may also encourage stakeholders to use existing COAs moving forward. Additionally, some COA tools are considered proprietary and thus not available for use by others. BIO thus requests the Agency indicate that it is acceptable for Sponsors to develop new COAs when there are no existing and reasonably *available* COAs.

Additionally, Figure 6 indicates that using a re-purposed instrument still results in every aspect of evidence development being required. This could be interpreted as requiring the same level of effort as de novo instrument development. We ask that the FDA consider modifying Figure 6 to indicate the ways in which using repurposing an instrument can be done more quickly, using less time and fewer resources than de novo instrument development.

3) Important considerations are needed for special populations, such as pediatric, the cognitively impaired, rare diseases, and patients from different language and cultural

groups. Does the Guidance 3 discussion document capture all the relevant special populations? What other populations should be identified for this FDA Guidance? Are there any other factors to consider when selecting, developing, and implementing COAs for these populations?

a. *What other factors need to be considered when determining a reasonable minimum age to self-report in a reliable and valid manner?*
b. *What other factors need to be considered when determining a reasonable minimum level of cognitive function to self-report?*
c. *How to address selection of COAs for people who move between a self-report status and inability to self-report?*
d. *What are other factors and/or approaches to consider when using COAs in multinational, multicultural, and/or multiregional studies?*
e. *Does the Guidance 3 discussion document appropriately present the important considerations for selection, development, and/or modification of COAs in rare diseases in sufficient detail and in a feasible manner? If not, what are other factors and/or approaches to consider?*

Utilizing COAs in pediatric patients or patients with rare diseases can be difficult because symptoms may present in different combinations according to the age of the patient and functioning impacts of these symptoms may also be significantly different. As such, further advice is needed on (a) how to adapt the measurement strategy to account for the most relevant/important symptoms among patients; and (b) how to measure the same latent construct (e.g., social functioning) in people where the components of this construct may differ (e.g., interactions among younger children and family members, interactions among friends and older children). Similarly, in the context of rare diseases, it is common for different symptoms/combinations of symptoms to present in patients at different points in time, even when a diagnosis/severity of disease is the same in these patients. Including "all symptoms" may dilute a treatment effect as some patients may not have a specific symptom. To this end, BIO requests that the FDA provide additional guidance on how to address heterogeneity in small samples for COA measurement. BIO appreciates that FDA recognizes there are challenges with selecting, developing, and implementing COAs for rare disease populations. For example, FDA recognizes that concept elicitation may be difficult to achieve in rare disease populations. However, FDA does not provide solutions. It would be helpful for FDA to build on further recognizing the challenges to note that for rare diseases with limited patient populations, concept elicitation would not be expected. Similarly, concept saturation would be difficult to conduct for rare disease populations and should not be expected. These can be replaced by innovative approaches to work within the targeted rare disease population.

Another special population to consider is patients with pre-symptomatic or early disease, where functional deficits may be minimal and may not progress significantly during the course of a trial. We believe there is value to using COAs in such patients (e.g., cognitive tests in patients with very early Alzheimer's disease) however it is unlikely that thresholds for meaningful change can be established using anchor based or qualitative methods. To this end, we request that the FDA acknowledge that approaches to measure meaningful

change may need to be more flexible in such patients. For example, in pre-symptomatic disease it may not always be necessary to link changes in a COA to changes in functional status observed during the trial. Instead demonstrating that changes in a given COA are associated with functional decline at a later stage in the disease (i.e. out of trial) or benchmarking against data collected from other interventional or non-interventional studies including real world data sources may be sufficient.

BIO appreciates that in the Discussion Document the Agency indicates that there may be cases when a symptom might best be reported using a combination of a PRO and an ObsRO (e.g., page 13, example using vomiting). To this end, BIO requests that the Agency provide greater detail regarding when it might be appropriate to use a PRO alone versus a PRO in conjunction with an ObsRO. Similarly, in Figure 4, the FDA indicates that an assessment may comprise a "PRO and/or ClinRO" and a physical performance measure may utilize a "PRO and/or performance outcomes measures (PerfO)". Additional advice from the Agency on how to best decide when to use a single measure versus multiple measures (e.g., disease severity, patient age, and other considerations) as well as how to combine both into a measurement strategy, would be helpful. Similarly, BIO also requests the Agency provide additional detail on the Cognitive impairment/non-verbal section. Such detail may include, for example, considerations of who should report on behalf of the patient. Much of this information is captured in Appendix 5 under the ObsRO section but it would be helpful if it was also referenced in the main body of the Discussion Document and/or expanded within the text.

Lastly, patients from different language and cultural groups are mentioned in this question, but they are not mentioned in Discussion Document 3.

4) Does the Guidance 3 discussion document capture the most appropriate and feasible methods to determine within-patient meaningful score changes in COA instruments? Are there any other methods to consider?

BIO appreciates that the interpretation section of Discussion Document 3 provides detail regarding thresholds for measuring improvement and decline, as within-person change definitions are relevant and important to provide context to indicate change from baseline. However, it would be beneficial for stakeholders if the Agency provided more detail regarding how such thresholds will be implemented using clinical trial data and which approach would be considered optional in various circumstances, for example through cumulative distribution plot, responder analyses, or time to event. We request that the Agency also consider presenting (a) within-group meaningful change definitions, and (b) between-group meaningful difference definitions. While the Agency alluded to such definitions in the Discussion Guide (e.g., boxed text, lines 1113-1126), it is unclear whether and how the Agency may make use of these data in review or decision-making. Additionally, the use of different and/or multiple anchors (e.g., as proposed in Table 4) usually provides a range of responder definitions, however a single definition best allows for the development of trial endpoints. BIO requests that the Agency provide additional information on how a range of responder definitions may be used to select a single value for an endpoint. Lastly, the Agency has indicated (e.g., line 699) that qualitative support should be provided to

demonstrate meaningful change. BIO also requests that the Agency provide additional insight on how this information should be generated and how it will be utilized by the Agency, either in lieu of or alongside quantitative estimates of meaningful change. Additionally, in the context of new disease areas or when using new measures it can challenging to obtain meaningful change thresholds for new PROs in advance of phase 3 clinical trials. To this end, we ask the Agency to allow for the use of alternative approaches in the context of Phase 3 trials, when applicable.

To encourage the development of other tools for collecting patient experience data, BIO requests that the FDA include a statement in the upcoming guidance that indicates that the FDA welcomes efforts to advance the science of patient-focused drug development, and that Sponsors are encouraged to seek to develop other, scientifically sound approaches to determining within-patient meaningful score changes as well.

5) Are there recommendations for any changes to the definitions we include for the categories of COAs (PRO, ObsRO, ClinRO, PerfO)? Are any additional categories of COAs recommended?

a. Digital monitoring sensors can be used for clinical outcome assessment (e.g., step counts collected via actigraphy). Please suggest approaches or methods to provide evidence of fitness for purpose (content validity, construct validity, reliability, ability to detect change) for these tools. For example, walking speed rather than step count may be most relevant and meaningful to a particular patient population.

BIO believes that the four categories mentioned above largely articulate the types of COAs available. BIO does however request that the FDA provide further clarity regarding PerfOs. Because, PerfOs may be administered by a trained individual or the PerfO independently completed by the patient, the Agency should clarify under what conditions a PerfO should be administered by a trained individual versus one that can be completed independently by the patient should be used. Additionally, it would also be helpful for the Agency to indicate how performance-based measures designed to be completed in the home environment (e.g., cognitive tests via apps, finger-tapping tests via phone sensors) may be considered PerfOs, but where independence may be assumed but cannot be confirmed/observed. Furthermore, it would be helpful for FDA to clarify when would sensor generated data be considered a new way of collecting data that is a PerfO.

As the Agency notes above, digital measures, including electronically administered PerfOs and passive monitoring, are increasingly being used in clinical trials and have the ability to collect important information from patients both inside and outside a clinical trial. To provide additional clarity around digital monitoring, BIO requests that the FDA further decipher types of digital monitoring into two categories:

- "standardized task" measures, where the patient is instructed to perform a specific task; and

- "monitoring" measures, where the patient is instructed to behave normally, and the patient is passively monitored.

It is unclear from Discussion Guide 3 the extent to which patient input will be weighed/considered when developing COAs versus that of clinicians and other data sources. For example, in Figure 3, "Conceptualizing Clinical Benefit" is defined as involving the identification of concepts of interest for meaningful clinical benefit (i.e., how a patient survives, feels (e.g., symptoms), functions). BIO requests that the FDA clarify how input from various individuals (e.g., patients, clinicians, caregivers) may be weighted and considered.

6) FDA strives to maintain flexibility in our evaluation of evidence, taking into account feasibility and practicality. Does the discussion document appropriately describe how FDA will assess whether a COA is fit for purpose?

As BIO mentioned above, we appreciate the reference to the use of existing PRO instruments in Discussion Document 3, whenever possible. However, the Agency suggests that concept elicitation can be completed using quantitative methods alone rather than in conjunction with qualitative methods. Additional information from the Agency on how quantitative data, without any qualitative data, should be collected, analyzed, interpreted and presented to the Agency.

It would be helpful to clarify who in FDA should be consulted in what types of instances, for example when developing a new tool or modifying an existing tool for a particular development program, or in a particular disease area or patient population, or general tool for potential use in various settings. Clarity of the process from FDA is important to the successful development and use of new tools or modification of existing tools.

7) Does the discussion document present information about best practices for COA selection, development, and/or modification in a manner that can reasonably and rigorously be implemented in medical product development?

The Discussion Document describes best practices and principles for COA development, adaptation, and appropriate use, however, it is unclear which of the best practices are recommendations and which are required prerequisites for Agency review. While it is important to allow flexibility to Sponsors in product development, some guidance on the "critical evidence" would help guide all stakeholders as they begin to develop COAs. For example, Table 2 (and subsequent text) suggests that the selection of concepts appropriate for a given trial should be informed by consultation with patients and/or caregivers, clinical, trial design, and measurement experts as well as via a literature review. One may assume that all of these items are required, but this may not be true where established concepts are proposed for measurement and endpoint specification. It would be helpful to specify what kind of data and information is expected to be submitted to the Agency to demonstrate that

the device or tool is fit for purpose. Additionally, further clarification regarding what documentation is needed when using "off the shelf" measure versus newly developed or adapted measure would also be beneficial.

We also recommend FDA to facilitate harmonization of different existing best practices developed by various independent entities such as professional societies. Such harmonization would enable standardization of practices and bring efficiency to the development of new tools. Further, clarification on the role of vendors in collection of patient experience data would be helpful.

8) Is the audience described for Guidance 3 appropriate? If not, what are recommended changes?

9) How do the good measurement principles presented in this discussion document apply to PerfOs and ClinROs, and what other evidence is needed?

a) There is existing literature related to PerfOs and ClinROs (e.g., PerfO White Paper and ISPOR Task Force ClinRO paper). Which principles from existing literature or other sources are important and appropriate for inclusion in FDA guidance?

We appreciate the FDA's additional guidance on observer-rated measures provided in Appendix 5 and would encourage a similar level of detail on ClinROs and PerfOs. In some sections the Agency has clearly identified differences in requirements for different types of COA (e.g., inter-rater reliability is required for ClinROs but not PROs) but further guidance, particularly around differences in determining content validity is needed. For example, it may not be appropriate to solely ask patients/caregivers about the conceptual relevance of performance-based tests, particularly cognitive assessments, and a clinician or other expert may be critical to understand how well the PerfO captures the concept of interest.

B. Additional Comments

- In Discussion Document 3 the FDA, indicates that it recommends measuring, at a minimum, core disease-related concepts (e.g., page 13); however, examples of "core" are not provided in the Discussion Guide. For example, there may be symptoms that are considered prevalent and bothersome, not reported by many patients, and others which are identified during qualitative research not considered as defining treatment benefit. To ensure consistency we request that the Agency define "core" disease related concepts and include the definition in the glossary moving forward. As FDA defines the "core" concepts, we encourage the Agency to encompass flexibility for Sponsors to select and describe the core elements for a patient population as the Sponsors design the individual development programs. Such flexibility is needed for pragmatic development so that only the relevant

elements are measured and elements that may not be relevant, e.g. elements that are not sensitive to treatment effect, are not needed to be measured.

- Throughout the Discussion Document there is inconsistency with respect to whether Institutional Review Board approval is needed. Often times, those wishing to conduct patient interviews/focus groups where patients are specifically recruited to gain patient input for COA development need to submit a protocol and discussion guide to the IRB, and a waiver or expedited review may be requested. BIO requests that the FDA clarify that IRB approval is required for obtaining patient experience data throughout the series of guidance documents.
- We would also like to express the need for alignment with and highlight for FDA's consideration the National Health Council's comments on the NIH & FDA RFI on Development of FDA Standard Core Clinical Outcome Assessments and Endpoints.

BIO appreciates this opportunity to submit comments regarding FDA's open docket on Patient-Focused Drug Development Guidance: Methods to Identify What Is Important to Patients and Select, Develop, or Modify Fit-for-Purpose Clinical Outcome Assessments. BIO is also working to collect and develop additional case examples that may help inform collection and utilization of patient experience data by all stakeholders. We would be pleased to provide further input or clarification of our comments, as needed.

Sincerely,

/S/
Danielle Friend, Ph.D.
Director, Science and Regulatory Affairs
Biotechnology Innovation Organization

Biotechnology Innovation Organization

III. SPECIFIC COMMENTS DISCUSSION DOCUMENT 2

SECTION	ISSUE	PROPOSED CHANGE
I. INTRODUCTION		
A. Overview and Scope		
Lines 84-85, Table 1, Overview of Content	In this section, the FDA states "Frame questions within the context of a participant's experiences; avoid questions about abstract or theoretical concepts". However, some questions may need to be framed hypothetically to ascertain patient preferences for future outcomes (e.g., treatment goals, meaningful improvement.)	BIO requests the FDA to consider the following edit: "Frame questions within the context of a participant's experiences; avoid questions about abstract or theoretical concepts, **when possible**".
Lines 84-85, Table 1, Overview of Content	In this section the FDA states, "Supplement interview data with other types of questions if data elicited is not useful," however, the approaches listed under this bullet may be planned approaches to elicit data and not considered supplementary or if elicited data is inadequate.	BIO requests the FDA to consider the editing the top bullet to indicate: "**Consider eliciting specific data by framing questions using targeted approaches, such as**…"
B. Questions FDA Has Identified for the October Workshop		
II. METHODS TO IDENTIFY WHAT IS IMPORANT TO PATIENTS		
A. Methodological Overview		
1. Concept elicitation		
B. Developing the Research Objectives and Questions		
Lines 175-178, Table 2	This section is focused on the considerations for researchers for framing questions related to the disease/treatment burden and the benefits and risks in disease management, however, the impact of a disease on a patient's daily life can be multi-dimensional. The guidance document would benefit from further elaboration on these points.	BIO requests that the FDA to expand the considerations listed under Burden of Disease to include the following: • Ability to work • Ability to carry out other tasks • Emotional and psychological functioning • Social skills

SECTION	ISSUE	PROPOSED CHANGE
		Also, under considerations for Burden of Treatment, we ask FDA to include treatment location (e.g., outpatient, hospital, in-patient).
1. Burden of disease/treatment and benefits and risks (harms) in disease management		
III. QUALITATIVE RESEARCH METHODS		
A. Sources of Qualitative Data to Elicit Burden of Disease and Treatment Benefits and Risks		
Lines 202-203	This section states "Gaining a more in-depth understanding of disease or treatment burden in order to develop clinical trial endpoints," but does not take into account the use of data to evaluate the adequacy of clinical trial endpoints.	BIO requests the FDA to consider the edit below: "Gaining a more in-depth understanding of disease or treatment burden in order to develop **or assess the adequacy of** clinical trial endpoints".
Line 207, Table 3	Here the FDA lists several types of data collection efforts as well as their associated advantages and disadvantages of each approach. However, while there are a multitude of different methods that could be appropriate, pragmatism and feasibility should also be taken into consideration.	BIO requests that the FDA to indicate in this section that the FDA encourage the use of the most pragmatic and feasible approach possible to achieve the intent.
Table 3-Focus groups disadvantages	This section states "Participants more likely to provide candid responses" as a stated advantage for focus groups, however it is unclear why patients would be more candid in focus group than one-on-one discussions.	BIO requests that the FDA remove this as a stated advantage. If not removed, BIO requests that the FDA consider revising the statement to read "Individual interviews should be considered as a methodology because participants may be more likely to provide candid responses on sensitive topics in one on one interviews." BIO also requests that the FDA indicate in this section that concept saturation is a disadvantage for focus groups and also indicate that for focus groups, a skilled facilitator or monitor may be required to improve the quality of answers.

SECTION	ISSUE	PROPOSED CHANGE
Table 3- Focus groups disadvantages	This section indicates that focus groups may result in large volumes of qualitative data that may be difficult to analyze.	BIO suggests removing this statement as large volumes of data can be generated regardless of whether the activity is a large focus group or one-on-one discussion and there are methods available to handle and analyze such data.
Table 3- PFDD Meetings	In this section on the advantages and disadvantages of PFDD meetings the FDA did not mention several other advantages of the PFDD meetings.	BIO requests the FDA to consider adding the additional advantages and disadvantages listed below. Advantages: Because of the larger group size more diverse topics may be discussed and a greater number of key opinion leaders may be present. Disadvantages: Because of the potential large size it may be more difficult for individuals to share their thoughts and less common opinions may be missed.
Table 3- Social Networks	This section is unclear, however we assume that the FDA is referring to collection of data through online social media sites.	For clarity, BIO requests that the FDA consider the follow edit: "**Collection of data through online** social media networks **and sites**"
1. Best practices for use of qualitative sources		
Line 272- Table 6	In this section on the advantages and disadvantages of in-person interviews the FDA did not mention several other advantages and disadvantages.	BIO suggests that the FDA consider including the following advantages and disadvantages: Advantages of in-person interviews: Allows the interviewer to use non-verbal cues (e.g., remaining silent as an indication that the participant should continue, which is awkward on the phone) Easier to build rapport and trust with the respondent

SECTION	ISSUE	PROPOSED CHANGE
		Disadvantages: Participants may be uncomfortable with in-person meetings with unfamiliar individuals (e.g. anxiety disorder, schizophrenia) or being interviewed in an unfamiliar environment such as a medical clinic. Travel distances and time may be a burden, particularly in rare diseases where patients are geographically dispersed.
Line 272, Table 6	In the section on video observation, the FDA does not mention issues pertaining to confidentiality and how patient privacy will be protected when using video observation.	BIO requests that the FDA include information on how confidentiality and patient privacy should be considered.
Line 272- Table 6	This section discusses using telephones for collecting information from patients but leaves out several key considerations that should be made prior to selecting telephones are the mode for collecting information.	BIO suggests adding reference to signal problems that may interfere with rapport building and understanding as well as reference to the consideration that participants may have limited access to telephones. BIO also suggests that the FDA consider expanding this to be "voice only data collection" which could be done using various technologies from land lines to cell phones and voice only services over the internet.
Line 272- Table 6- Advantages to video conferencing	In this section on the advantages and disadvantages of video conferencing the FDA did not mention several other advantages and disadvantages.	BIO requests that the FDA consider adding to the advantages for video conferencing.
Lines 320	In this section, the FDA outlines examples of approaches for asking patient different questions; however, almost all of the examples could be	BIO requests that the FDA provide example questions in this section that would be more appropriate for lower literacy levels.

SECTION	ISSUE	PROPOSED CHANGE
	employed in qualitative research are written for relatively higher literacy/health literacy levels.	
Line 330	Early trial participants are likely not representative of the final target population for Phase 3 trials or those likely to use the marketed product.	BIO requests that the FDA indicate in the 'Limitations" section that trial inclusion/exclusion criteria (especially if an early-phase trial) may significantly limit the generalizability of the input.
Lines 359-260	This lines states "Be patient and allow the respondent to gather their thoughts, control their emotions, and find the words to describe their experience," however this is the first reference to cognitive debriefing.	BIO requests that the FDA include the terms "cognitive debrief" in the glossary. We also suggest that the FDA use consistent terminology for cognitive debrief in future discussion guides and guidance, including Discussion Guide 3 and provide a reference to best practices for cognitive debriefing.
IV. QUANTITATVE RESEARCH METHODS		
A. Sources of Quantitative Data to Elicit Burden of Disease/Treatment and Benefits and Risks		
1. Best practices for use of quantitative sources		
Lines 472	This section states "Testing questions to make sure they can be answered as intended," but it is unclear as to whether this is referring to cognitive debriefing, pilot testing questions, probing further to ensure comprehension, or interpretation or response options?	BIO asks the FDA to clarify this section.
Lines 487-489	This section states "When designing questions for surveys/questionnaires, you should design questions to be good measures to maximize the relationship between the answers recorded and what you are trying to measure."	For clarity, BIO asks the FDA to consider removing this section or including the following edits: "~~**When**~~ designing **good** questions **and response options** ~~**for surveys/questionnaires, you should design questions to be good measures to**~~ maximize**s** the

SECTION	ISSUE	PROPOSED CHANGE
		relationship between the answers recorded and ~~what~~ **the concept** you are trying to measure."
Lines 463-506	Many of the elements included in this section apply to both qualitative and quantitative methods.	BIO suggests including these points in the qualitative section and then referencing to them in the quantitative section or developing an entire section that includes considerations for both qualitative and quantitative methods.
Lines 523- Table on Advantages and Disadvantages of Open and Close-ended Questions	This section indicates that open-ended questions may produce rare answers that cannot be analyzed in a useful manner, however rare answers can be informative. Suggest reframing to "Less common answers can be challenging to analyze"	BIO requests the FDA to consider using language that indicates "Less common answers can be challenging to analyze and should be considered individually".
Lines 536 Table, Dichotomous Responses	This section indicates that dichotomous responses may force respondents to choose between options that may not be that simple, resulting in a response that doesn't completely capture their experience/feelings and limits the analysis that can be performed. However, these items are only limitations if dichotomous responses are used inappropriately.	BIO requests the BIO remove these two bullets or provide greater clarity under which circumstances limitations may occur.
V. MIXED METHODS		
VI. CONCLUSIONS		
VII. REFERENCES		
VIII. Appendix		
Appendix 2 – Considerations for Special		BIO suggests acknowledging that adding in specific tasks such as drawing or other communication aids may enable

SECTION	ISSUE	PROPOSED CHANGE
Populations and Cultural Differences for Qualitative Studies		those with impaired functioning to participate, even if this is in conjunction with a caregiver.

Biotechnology Innovation Organization

IV. SPECIFIC COMMENTS Discussion Guide 3

SECTION	ISSUE	PROPOSED CHANGE
I. INTORDUCTION		
A. Questions FDA Has Identified for the October Workshop		
II. OVERVIEW AND SCOPE		
Lines 205-208	This section indicates "….as well as certain COAs derived from technologies, such as mobile health technologies (e.g., activity monitors, sleep monitors) that do not fall into one of the other types of COAs.	As mentioned above, BIO requests that the FDA separate PerfOs into those that are standardized tasks and those that involved observation or passive monitoring. BIO also requests that the FDA provide examples of when such technologies would and would not be considered a COA.
III. BACKGROUND		
IV. CLINICAL OUTCOME ASSESSMENTS IN MEDICAL PRODUCT DEVELOPMENT		
Lines 283	This section indicates that "The COA validly and reliably measures concepts that are clinically relevant and important to patients" but this section does not include reference to caregivers.	BIO requests the following edits: "The COA validly and reliably measures concepts that are clinically relevant and important to patients **and caregivers**"
Line 300, Figure 2	This section outlines three different pathways for regulatory advice depending upon what is trying to be accomplished.	BIO requests that the FDA add examples to support when each pathway could be used and clarify that Critical Path Innovation Meetings are non-binding meetings.
V. ROADMAP TO COA SELECTION/DEVELOPMENT FOR CLINICAL TRIALS		
Lines 330, Figure 3	This section outlines the roadmap for COA selection/development for clinical trials.	BIO requests that the FDA consider the following edits: Column 1: • 1B, consider adding "by age" • 1B, consider adding "genotype"

SECTION	ISSUE	PROPOSED CHANGE
		• 1D, clarify that the definition of clinical benefit should be from the patient perspective, when feasible and available • 1D, add "frequency", "severity", and "nature of symptoms" Column 2: • 2D, consider adding current unmet needs • Consider adding "in the context of the mechanism of action" Column 3: • 3C, consider renaming the title to 'Develop, Evaluate and Document the COAs:' BIO also requests that the FDA add clarify where sensors fit into the roadmap in section 3A.
Line 331 Roadmap footnote	It is not clear how engagement with FDA early and throughout the medical product development can be done efficiently to fit the development timelines and logistically (i.e., are there other pathways besides Type B/C meetings?). Further, if the PED/PFDD discussion should occur within the standard 1-hour development meeting, there most often would not be enough time for discussion.	Please see BIO's response to question 9 (page 8) posed by the FDA pertaining to question 9 on page 46 of this letter will address this issue.
Line 332 Roadmap Note	This section indicates that the roadmap can also be used to conceptualize tolerability or risk but does not	BIO requests that the FDA provide examples as to how the roadmap may also be used to assess tolerability or risks.

SECTION	ISSUE	PROPOSED CHANGE
	indicate how the roadmap be used to assess tolerability or risk.	
Line 356 Table 2	This section provides details on conceptualization of clinical benefit but does not reference the caregiver's role in understanding aspects of a disease.	BIO request that the FDA consider adding 'caregivers' to the table to indicate that they may have input on aspects of the disease.
Lines 379-386 Concepts related to tolerability, safety, burden	Discrepancies between patient-reported AEs and physician-reported AEs continue to be a concern of industry as the compliance implications, whether a Sponsor must attempt to reconcile discrepant reports, and exactly what a Sponsor should report to FDA.	Please clarify if symptomatic adverse events collected from patients need to be reconciled with those collected from physicians through spontaneous AE reporting guidelines. Also, please clarify if Sponsors have additional reporting responsibilities when collecting symptomatic AEs from patients.
Line 397 Targeted labeling claim(s)or communication	This bullet states "Targeted labeling claim(s) or communication" but it is unclear what "communication" refers to.	BIO requests that the FDA clarify what is meant by "communication."
A. Understanding the Disease or Condition		
B. Conceptualizing Clinical Benefit		
1. Concepts of interest		
2. Context of use		
Line 442 Figure 4	This chart includes a reference to supportive endpoints.	BIO requests that the FDA clarify if "Supportive" is equivalent to "Secondary."
Lines 442, Figure 4	This section provides an example of endpoint positioning, however, it is unclear to the reader what the FDA means by "supportive endpoints".	BIO requests that the FDA clarify that "supportive endpoints" is intended to encompass both secondary and exploratory endpoints.
C. Selecting/Developing a COA		

SECTION	ISSUE	PROPOSED CHANGE
Lines 476, Table 3	The first half of table (COA type) discusses what is included in the text below, outside of the Table.	BIO requests that the FDA either reference the text in the Table, or expand, or remove table.
Lines 476, Table 3	This section details considerations for COA measurement properties but does not include appropriateness of scoring algorithms to measure COA properties.	BIO requests that the FDA add appropriateness of scoring algorithm to COA measurement properties.
1. Selection of COA type		
Lines 495	This section indicates that PerfOs measure may be used to assess patient functioning (e.g., physical, cognitive, or perceptual/sensory functioning) but does not address passive monitoring observation (using video, digital devices, etc).	Consider adding passive monitoring using digital devices (e.g., tremor in PD may be captured without a standardized task).
2. Evaluation and documentation of COA development history		
Lines 515	This section indicates "The goal of pilot testing COAs is to select and/or refine a COA to be carried forward into registration trials to establish product effectiveness."	BIO requests that the FDA consider making the addition: "The goal of pilot testing COAs is to select and/or refine a COA **and its associated scoring algorithm** to be carried forward into registration trials to establish product effectiveness."
3. Search strategy for COA		
Line 531	This section indicates that "It is important to note that some instruments used widely in clinical practice might not be fit-for-purpose for regulatory trials as they may not be designed in a way that would make it likely to be sensitive in detecting treatment effects and discriminating between treatment and placebo arms' scores."	For clarity, BIO requests the following edits: "It is important to note that some instruments used widely in clinical practice might not be fit-for-purpose for regulatory trials as they may not be ~~**not be designed in a way**~~ sensitive in detecting treatment effects and discriminating between treatment and placebo arm scores **or they may**

SECTION	ISSUE	PROPOSED CHANGE
		not measure meaningful aspects of how a patient feels or functions or they may not be patient-centered."
Lines 550, Figure 6	This figure does not address existing COAs that were developed for the intended context of use (COU) but that were not necessarily developed well.	BIO requests that a box be added where the Sponsor assesses if the existing evidence for the COA in the intended COU is adequate for its use with no additional work needed. If not, additional evidence may need to be generated in Steps II-IV, and instrument modification may be needed. As part of II suggest adding "Check that license holder will allow modification of an existing instrument
Line 550 Figure 6	This section references "original COA" but the use of the term is unclear in some places. For example—"Use the existing COA, no additional work needed" and "Use the existing COA, as is" imply no additional work, but the 2 boxes use different language.	BIO requests that when possible the FDA use consistent language and clarify what is meant by "original COA" vs "existing COA" in these 2 contexts.
Line 550, Figure 6	The box at the bottom of the figure uses the words "steps" but "steps" implies a sequence and not all "steps" may be required.	BIO requests that the FDA reword this box to reference "points," "elements", or "process" rather than "steps". For clarity, we also ask the FDA to differentiate between new COAs vs modified COAs.
VI. EVALUTAION OF A CLINICAL OUTCOMES ASSESSMENT		
Lines 611-626	This section outlines characteristics that are reviewed by the FDA within the medical development program, however content validity has much more detail than the psychometric properties that may be included within the bullet labeled "other".	Because the information from these bullets are discussed in detail in the following sections, we suggest removing the sub-bullets so that it is clear that the measurement properties are as important as content validity (i.e., a COA cannot be adequate for use in clinical trials if content validity is documented but its measurement properties are not).

SECTION	ISSUE	PROPOSED CHANGE
A. Conceptual Framework		
Line 644	As mentioned above, greater clarity is needed for circumstances when different types of COAs are the most appropriate.	Suggest a specific section on PerfOs is required that acknowledges that in certain circumstances, clinical experts need to be consulted to validate that the link between the task itself and the symptom (e.g., patients may report slow thinking and so an appropriate test might be the Symbol Digit Modality Test).
B. Evidence of Content Validity		
Line 672	In this section the FDA indicates that content validity should be supported by evidence obtained from qualitative studies, . . . quantitative studies (e.g. descriptive statistics and other measurement properties), however, it is unclear what is meant by measurement properties.	BIO asks the FDA to clarify what is meant by other measurement properties in this section.
Line 680	This section indicates "For more complex concepts, a greater the number of patients may be needed in qualitative studies to adequately understand that concept and how it varies across the target population."	BIO suggests the following edit for clarity: "For more complex concepts, a greater the number of patients may be needed in qualitative studies to adequately understand that concept and how it varies across the target population **to achieve saturation**".
Line 689	This section indicates "Examples of information that should be submitted to establish content validity include the following:"	For clarity, BIO requests the following edits: "~~**Examples of**~~ The information ~~**that should be submitted**~~ **required** to establish content validity **will depend on the COA type but may include**".

SECTION	ISSUE	PROPOSED CHANGE
Lines 699-700	In this section the FDA indicates that qualitative support for meaningful change and quantitative evidence to support item retention and scoring are components of or indicators of content validity, however statement does not align with the definition of content validity provided in the agencies BEST glossary which states "A process to establish from qualitative research the extent to which the clinical outcome assessment instrument measures the concept of interest including evidence that the items and domains of an instrument are appropriate and comprehensive relative to its intended measurement concept, population, and use".	BIO requests that the agency provide additional information on how and why these should be considered as evidence for/indicators of content validity.
1. Intended population		
2. Concept elicitation		
3. Item (question or task) and content generation		
Lines 756	This lines indicates "Items should be relevant to most of the patients in the clinical trial," but there is little detail regarding what "relevant" means in this context.	BIO requests that the FDA consider the following edits: "Items should be relevant to most of the patients in the **condition being studied in the** clinical trial **(e.g. a symptom impact that most patients experience or aspire to seeing improvement on).**"
4. Cognitive interviews		
Lines 765	This section states "understanding of the COA can be evaluated through cognitive interviewing with relevant stakeholders," but does not provide information regarding what the relevant stakeholders are.	BIO suggests that the FDA provide examples regarding relevant stakeholders in this context by including the following edit: "understanding of the COA can be evaluated through cognitive interviewing with relevant stakeholders **(e.g. for a clinRo this might be the clinician and the patient).**"

SECTION	ISSUE	PROPOSED CHANGE
Lines 775	This section indicates "concepts included in the conceptual framework are confirmed," but no examples are provided.	BIO requests that the FDA provide an example of how this might be demonstrated for a PerfO and clinRo.
5. Data collection mode and type of COA administration		
6. Language translation and cultural adaptation		
7. Recall period (if applicable)		
Lines 824		It would help to have more detail on time window for passive monitoring. Are there any recommendations on whether things should be measured continuously over the course of a trial or if chunks (e.g. of one week) could be appropriate
8. Response options		
Lines 855-861	The description of card sorting in the paragraph followed by the use of it in the example makes it seem like this method is strongly preferred.	To mitigate the interpretation that card sorting is the preferred method, BIO requests the FDA to consider redesigning the paragraph to be more general or offer alternative methods to evaluate response options (e.g. item response theory) to allow flexibility to select the method that is most appropriate for the study.
9. COA format, instructions, and training		
Lines 897	This section indicates "It is important that the instrument format used in the clinical trial be consistent with the format that is used during the COA development process. Format refers to the exact questionnaire, diary, or interview script appearance used to collect the COA data. Format is specific to the type of COA administration and the data collection mode." However, it implies that a draft PRO to be used electronically would need to be administered as ePRO for the cognitive debriefing interviews - which	To address this issue, BIO suggests the follow edit: "~~**It is important that**~~ **Ideally** the instrument format used in the clinical trial would be consistent with the format that is used during the COA development process. Format refers to the exact questionnaire, diary, or interview script appearance used to collect the COA data. Format is specific to the type of COA administration and the data collection mode.

SECTION	ISSUE	PROPOSED CHANGE
	should be an iterative process, and may result in months between each round as the device is reprogrammed. Suggest changing from "It is important that" to "Ideally"	
10. Respondent and administrator burden		
Lines 940-941		To clarify this section, BIO requests the FDA to consider adding a statement such as: "**To avoid excessive burden, the COA could be evaluated by cognitive debriefing**".
11. Scoring of items and domains		
C. Evidence of Other Measurement Properties: Reliability, Construct Validity and Ability to Detect Change		
1. Reliability		
Line 1020	In this section the FDA indicates that test-retest is required to demonstrate reliability. However, in some trial settings it is not feasible to evaluate test-retest reliability (e.g., acute disease conditions, rapid-acting treatments).	BIO requests that the FDA indicate that test-retest is not always feasible.
Line 1031	This section indicates that "for COAs or study design where the same rater will rate several patients, it may be necessary to examine the intra-rater reliability. A COA demonstrates adequate intra-rater reliability when there is high agreement among COA ratings by the same rater on multiple patients of the same disease condition" however, the example could benefit from clarity as it currently references intra-rater reliability by referring to different patients, not different raters.	BIO requests the FDA clarify this statement.

SECTION	ISSUE	PROPOSED CHANGE
2. Construct validity		
3. Ability to detect change		
Lines 1086	This section states that "the ability of a COA to detect change may influence the calculation of sample size for evaluating the effectiveness of treatment. In general, an inability of a COA to detect change tends to support the null hypothesis of no treatment effect."	For clarity, BIO requests that the make the following edit: "The ability of a COA to detect change may influence the calculation of sample size for evaluating the effectiveness of treatment. In general, an inability of a COA to detect change tends to support the null hypothesis of no treatment effect **for example when the COA is a primary outcome measure**"
D. Interpretation of meaning of change		
Lines 1098-1099	This section indicates "As such, special consideration should be given by the Sponsor to assess how meaningful the observed differences are likely to be," but there is no definition of observable difference.	BIO requests that the FDA clarify the terms "observed differences".
Line 1124-1125	This section indicates "additionally, the minimum change may not be sufficiently to serve as a basis regulatory decisions."	For clarity, BIO requests the FDA to consider the following edit: "~~**Additionally, the minimum change may not be**~~ **Demonstrating between groups differences may not be** sufficient~~**ly**~~ to serve as a basis for regulatory decisions".
Line 1128 Anchor-based Methods	This section provide information on ancho-based methods to establish within-patient change but for existing COA measures, it is not clear at what point Sponsors should perform anchor-based analyses (e.g./ interim-blinded data vs end-of-trial after unblinding)	BIO requests that the guidance reference existing COA measures and at what point Sponsors should perform anchor-based analyses. We also request that the FDA indicate in the guidance that for certain therapeutic areas (e.g., oncology) "no change" might be meaningful to patients.

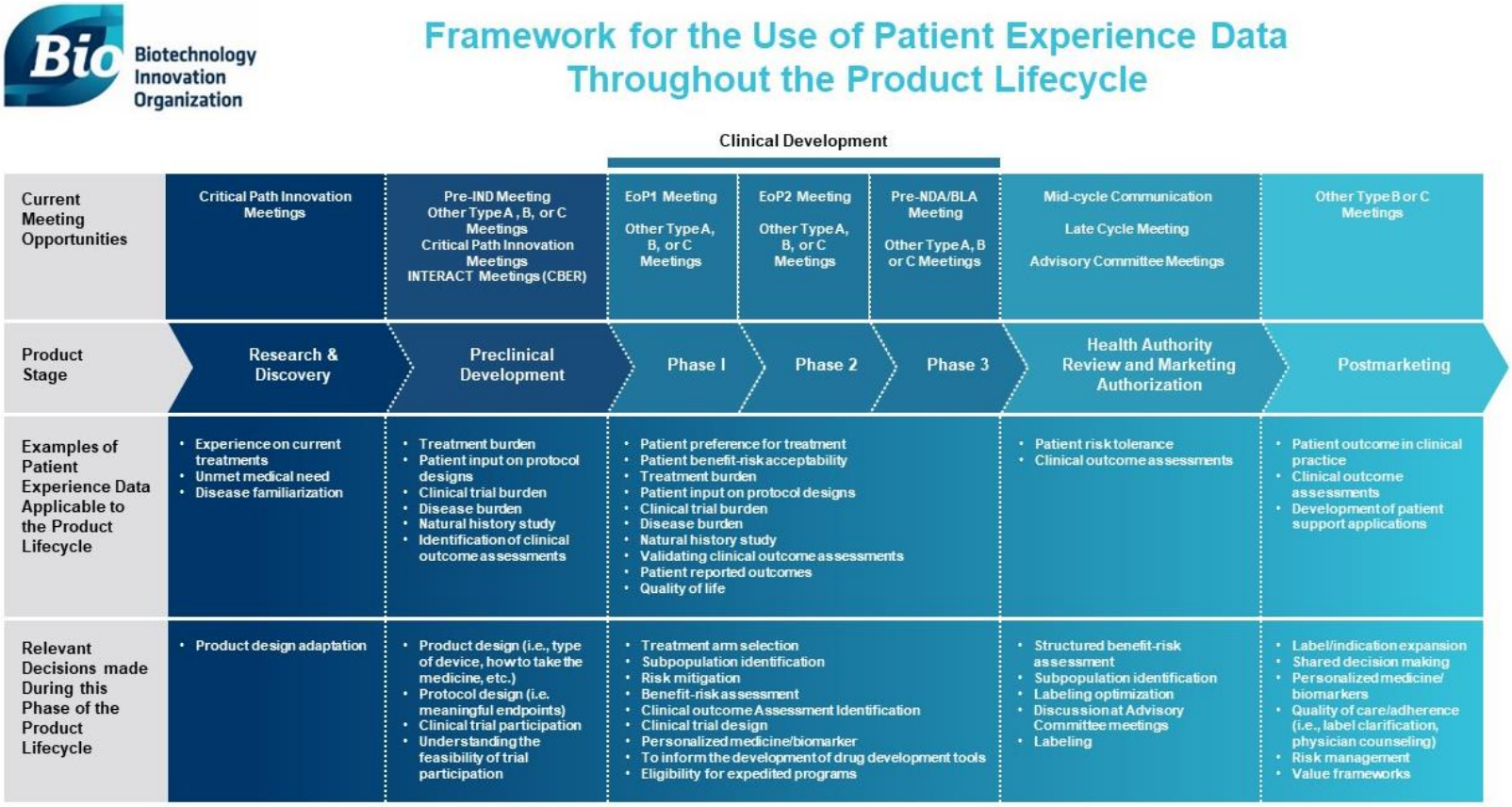
SECTION	ISSUE	PROPOSED CHANGE
	Also, recognition should be included that in certain therapeutic areas (e.g., oncology) 'no change' might be meaningful to patients.	
1. Anchor-based methods to establish meaningful within-patient change		
Lines 1142	This section states "Well-established clinical outcomes (if relevant)"	BIO requests the FDA to make the following addition: "Well-established clinical outcomes (if relevant) **(e.g., acquisition of a motor milestone).**"
Lines 1142, Table 4	This section states "A static, current state global impression of severity scale is recommended at minimum, when appropriate, since these scales are less likely to be subject to recall error than global impression of change scales; they can also be used to assess change from baseline"	BIO suggests that the FDA include two bullets on anchors: One that addresses the preference for severity over change regarding recall, and another anchor indicating change if preferred over severity for slow progressive disorders where severity may not capture small meaningful changes but the change measure does.
Lines 1142	This section indicates that "Selected anchors should be plainly understood in context, easier to interpret than the COA itself, and sufficiently correlated to the targeted COA," but no definition is provided for the terms "sufficiently correlated."	BIO requests that the FDA define "sufficiently correlated".
2. Using empirical cumulative distribution function (eCDF) to supplement anchor-based methods		
3. Other methods		
VII. CLINICAL TRIAL DESIGN CONSIDERATIONS		
A. General Protocol Considerations for COA Endpoints		
1. Endpoint Definition(s)		
B. General Protocol Considerations for Blinding/Masking		
1. Blinding (Masking)		
C. Frequency of Assessments for COA Endpoints		

SECTION	ISSUE	PROPOSED CHANGE
Lines 1277	This section provides information on the timing of the anchor scale administration.	In addition to aligning timing of the administration of the anchor scale with the COA, the timing should also allow for the recall period of both the anchor scale and COA to be aligned.
D. Clinical Trail Duration for COA Endpoints		
E. Design Considerations for Multiple Endpoints (Including COA Endpoints)		
F. Use of Electronic Mode of Administration		
Lines 1301	This section outlines advantages of electronic data capture but does not discuss possible disadvantages.	BIO suggests providing advantages as well as disadvantages of electronic data capture.
1. eCOA selection		
2. Paper-electronic migration and equivalence		
3. Device validation		
4. Data-related regulatory considerations		
VIII. DATA ANALYSIS		
A. General Statistical Considerations		
B. Multi-Component Endpoints		
Lines 1473-1483	Both composite endpoints and multi-component endpoints are referenced in this section however, only multi-component COA endpoints are discussed. It would be helpful to also include an example of a COA-based composite endpoint to help understand the distinction.	BIO requests that the FDA also include an example of a COA-based composite endpoint to help understand the distinction.
C. Patient-Level Missing COA Data		
1. Missing items with domains		
2. Missing entire domains or entire measurements		
SPECIAL PATIENT POPULATION CONSIDERATIONS		
A. Rare disease patient populations		

SECTION	ISSUE	PROPOSED CHANGE
Lines 1532-1533	The document states "Rare disease often need more sensitive outcome measures to quantify disease." This is typically because sample sizes are small and so it is harder to show statistically significant changes. This could be misinterpreted that acceptable measurement properties in rare disease must meet more stringent requirements.	BIO requests that the FDA further clarify and recommends the following edit: "Rare diseases often need more sensitive outcome measures to quantify disease **due to the small sample sizes in clinical trials**."
B. Pediatric Patient Populations		
Lines 1619-1620	This section should include suggestions on helping children completing COA independently.	BIO recommends that the FDA add voice technology and other innovative technologies to enable young children to respond on their own. By providing examples, including interactive voice technology, it keeps the guidance flexible for new technology that may enable children to complete PRO on their own.
C. Patients Cognitively Impaired or Unable to Communicate (non-verbal)		
Lines 1642	This section outlines considerations when working with patients with cognitive impairments but the section lacks important detail about how to address such challenges.	BIO requests that the FDA provide more information for example considerations of who should report of behalf of the patient, and in what circumstances both a PRO and ObsRO may be appropriate.
Appendix 1, Section IV, line 111 Qualitative data that supports content validity	Re: The last bullet on 'interpretation' Qualitative data are not typically used to support scoring of the instrument. Scoring is usually supported through the psychometric analyses. However, qualitative data can be used to get a preliminary understanding of the degree of change considered clinically meaningful by patients.	We suggest changing the last bullet to 'interpretation' instead of 'scoring."

SECTION	ISSUE	PROPOSED CHANGE
Appendix 1, Section VII, line 178 Translation & Cultural Adaptation	Ensuring that content validity and other measurement properties are comparable between the original and 'new' instruments (assuming that refers to translated versions?) would be extremely difficult to do, given small sample sizes.	As an alternative, we suggest the wording is revised to give flexibility around the translated versions and possibly refer to statistical analyses in the context of the clinical trial that can be used to confirm there are no differences in results across countries or regions.
IV. REFERENCES		

V. Chart Outlining Types of Patient Experience Data and Decisions for which Patient Experience Data can Help Inform



VI. Case Examples Demonstrating Types of Patient Experience Data and Drug Development and Review Decisions that Such Data can Inform

The examples provided here are meant only as specific illustrations in the particular scenarios and do not represent all types of scenarios and development programs.

A. Patient Experience Data Collected to Inform Clinical Trial Design

Case Example 1:

Purpose of BIO Including this Case Example:

- The case example demonstrates ways in which patient experience data can be used by a Clinical Development team (in this case, clinical trial design).
- The case example demonstrates that the evidentiary standards needed for the patient experience will vary depending upon the intended use of the data
    - This case example demonstrates patient experience data used for clinical trial design, whereas case example two (page 42) demonstrates how evidentiary standards may be different for patient experience data used for endpoint development.

Reason for Collecting Patient Experience Data in Case Example 1:

To Inform Clinical Operations:
In order to make clinical operations more patient focused and to use patient experience data to help inform clinical trial design, a series of focus groups were conducted for women who had breast or ovarian cancer and had participated in a clinical trial. Some of the questions we asked of the participants included:

- Was there any information that would have made your decision to participate easier?
- What about the trial that you participated in would you have changed if you could have?
- Now that your participation in the trial is over, what do you know now that you wish you would have known before you began?
- Did you feel that your participation was appreciated or made a difference? If "no", what could have been done to change that?
- What kind of information/communication would you have liked after your participation in the trial ended? Would you have appreciated communication from the study Sponsor?

To Inform Clinical Trial Design:
In order to use patient experience data to help inform clinical trial design, patients, care partners, and advocates were identified via relevant advocacy organizations. The company introduced their plan to the patient organization and the patient organization helped identify potential patients who might fit the criteria outlined by the company conducting the study.

Identified patients were contacted electronically and were asked to review the draft protocol and provide input on topics such inclusion and exclusion criteria, potential concerns that participants might have regarding the schedule of events, potential needs that participants

might have for support, and study elements that were unnecessarily burdensome during the study and the follow-up.

Evidentiary Standards Used:
No evidentiary standards were used for collection of this set of patient experience data.

Outcome:
Input from patients has resulted in additional detail regarding dose modifications and adverse events, consolidation of visits, clarification of biopsy requirements. Additionally, informed consent language has been modified. An unexpected benefit was the gratitude shown by the patients who participated in reviewing of the materials for the opportunity to "give back."

B. Patient Experience Data Collected to Inform Endpoint Section

Case Example 2:

Purpose of BIO Including this Case Example:

- The case example demonstrates ways in which patient experience data can be used by drug developers (in this case example, patient experience data are used to inform endpoint development).
- The case example demonstrates that the evidentiary standards needed for the patient experience will vary depending upon the intended use of the data
    - This case example demonstrates patient experience data used for endpoint development, case example 1 demonstrates how evidentiary standards may be different for patient experience data used for endpoint development.

Reason for Collecting Patient Experience Data in this Case Example:
Hidradenitis suppurativa (HS) is a painful, chronic skin disease characterized by recurrent inflamed nodules and abscesses, which often rupture to form fistulas and subsequent scarring. Its impact on patients' quality of life is profound. Until 2015, there were no approved medical therapies for this orphan condition nor were there ways to reliably measure clinical improvements for this disease. As part of its the drug clinical development program, the Sponsor developed and validated a new primary endpoint called Hidradenitis Suppurativa Clinical Response (HiSCR) to measure disease improvement in patients diagnosed with moderate-to-severe HS, showing it to be a meaningful (both clinically and to the patient), valid and reliable instrument in this orphan population.

Evidentiary Standards Used:
Prior to the development and validation of HiSCR to assess treatment response, the Sponsor used other instruments, such as the modified Sartorius scale (MSS) and Hidradenitis Suppurativa Physician Global Assessment (HS-PGA), as a primary endpoints in a Phase 2 trial of moderate-to-severe HS patients. However, the MSS scale was time-consuming and difficult to interpret and could include body regions that were not impacted by the disease leading to uncertainty in scoring. The HS-PGA failed to adequately distinguish between the severity levels of the disease and heterogeneity within severe patients created the possibility that patients could experience clinically important improvement but not gain a meaningful reduction in their HS-PGA score. Therefore, HiSCR was developed and validated to address some of the limitations associated with use of MSS and HS-PGA and eventually served as the primary endpoint in the phase 3 trials upon which the product was approved for HS.

To demonstrate the validity and meaningfulness of the tool, psychometric properties of HiSCR were not only evaluated based on physician-rated severity measures (i.e., MSS, HS-PGA, and Hurley staging), but were also evaluated against patient-reported measures to capture the patient perspective. In that regard, three patient-reported outcome (PRO) instruments, included in Phase 2 study, were used to demonstrate the association between HiSCR response criteria and PRO results: the Visual Analogue Scale for HS skin pain (Pain

VAS), the Dermatology Life Quality Index (DLQI), and the Work Productivity and Activity Impairment Questionnaire: Specific Health Problem (WPAI:SHP). The definition used to define meaningful response using HiSCR (i.e., 50% reduction in AN count with no increase in abscess and draining fistula) was associated with an improvement in patient reported outcomes as well.

Outcome:
The validation of the tool was assessed against outcomes important to patients. This new endpoint, HiSCR, is available to other Sponsors who wish to develop new therapies to treat HS. A recent query of the ClinicalTrials.gov database found that indeed other Sponsors are using the HiSCR as an endpoint in HS trials*.

C. Dyad Interviewing Technique for Determining Concepts of Interest to Support Treatment benefit Endpoints in Pediatrics (ObsRO or PRO)

Case Example 3:

Purpose of BIO Including this Case Example:

- Demonstrates ways in which patient experience data can help inform when a patient reported outcome versus an observer reported outcome should be used.
- Provides concrete solutions and considerations for collecting patient experience data from pediatric populations, similar examples may be provided for other special populations.

Reason for Collecting Patient Experience Data in this Case Example:
Dyadic interviewing is a qualitative approach that recognizes there exists an interdependent relationship between individuals, embracing this phenomenon as a source of information rather than attempting to control for it. The dyadic interview technique can be employed to address some of the difficulties that present when conducting interviews with pediatric populations to understand at what age they are able to self-report via patient-reported outcome (PRO) and if not, what are the appropriate concepts to be assessed through an observer-reported outcome (ObsRO). The interview structure consists of a dyad that includes the child with the condition of interest and their parent or the person identifies as their legal guardian.

Important aspects to consider and investigate, include:

- Determining the "breakpoint" age for self-report as well as the complexity of the disease consequences (i.e. amount of self-insight and developmental maturity required) to be evaluated (e.g. emotional consequences may be more difficult for a child to articulate).
- Concordance of disease consequences reported by the child and the parent/guardian (i.e., is this truly a consequence of concern to the child and what matters to the parent) or is it a consequence of concern to the parent (e.g., a child who can't sit still at the dinner table may not see that as a concern to themselves but the parent does).
- If it is determined that the concept of interest is not reportable by the patient (e.g., child at or below a certain age), how does the consequence manifest as something observable to the parent/guardian?
- Are there important disease consequences that could be omitted from an outcomes measure because they are not observable to a parent/guardian and the child is not able to self-report?
- Is the window of time in which a parent has the opportunity to observe a disease consequence representative (e.g., is the consequence manifesting when the parent cannot directly observe such as during the school day when a parent is at work?)