ISPOR
The professional society for health economics and outcomes research

Improving healthcare decisions

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September 10, 2018

Dr. Scott Gottlieb
Food and Drug Administration
10903 New Hampshire Ave
Silver Spring, MD 20993-0002

Dear Dr. Gottlieb:

ISPOR – the professional society for health economics and outcomes research - is pleased to respond on behalf of its membership to the U.S. Department of Health and Human Services Food and Drug Administration's call for comments on "Patient Focused Drug Development: Collecting Comprehensive and Representative Input." We strongly agree that these are important issues to address with input from a wide variety of stakeholders and thank the Department for this opportunity to provide our comments.

ISPOR is a scientific and educational society with many of its members engaged in some aspect of health economics and outcomes research (HEOR) related to evaluation of pharmaceuticals. Patient focused research is a key area of interest for HEOR professionals. Our membership includes over 20,000 individuals across a range of disciplines, including health economics, epidemiology, public health, pharmaceutical administration, psychology, statistics, medicine, and more, from a variety of stakeholder perspectives, such as the life sciences industry, academia, research organizations, payers, patient groups, government (including some HHS/FDA employees), and health technology assessment bodies. The research and educational offerings presented at our conferences and in our journals are relevant to many of the issues and questions raised in this request for information.

We have chosen to respond to selected sections where we felt strongly about the recommendations or methods. This response was formulated with the assistance of ISPOR's most representative scientific membership groups: the Clinical Outcomes Assessment, Patient Centered, and Stated Preference special interest groups, the Health State Utility task force, as well as our Patient Representatives Roundtable and Institutional Council. It was reviewed by and approved by our current President and myself.

ISPOR would be happy to answer any questions about our response to Guidance 1, as well as to participate in any follow-up consultations on Guidance 1 or any of the forthcoming guidance documents in the series.

Sincerely,

Nancy S. Berg
CEO & Executive Director
ISPOR

General Comments on Guidance 1:

This document introduces the guidance series on Patient Focused Drug Development (PFDD) and explicitly addresses PFDD sampling methods. Overall the document is well written and scientifically sound. We offer a number of specific comments below for consideration that we believe will add clarity.

Specific comments by section:

Overview of the Series of FDA Guidance for Enhancing the Incorporation of the Patient's Voice in Drug Development and Regulatory Decision Making (Line 21)

We recommend that the introduction clearly outline the benefits of including patient experience information for both patients and manufacturers. For example, will the data be described in the label to advise other patients? Are there any consequences for not collecting and reporting this information? The document is rich in technical terms but lacks a view how it can aid healthcare consumers (patients and caregivers).

Patient Experience Data (Line 155)

1. Table 1. (line 187) Types of Patient Partners: These terms and definitions of what it truly means to involve patients "not only as study subjects but as partners" have been defined by other organizations such as EUPATI. The Agency should clearly define what this kind of engagement will look like in the US setting and explore whether it can leverage other definitions already out in the public space. Consider including examples that reflect this idea in this section.

2. *Impact of the disease and its treatment (line 194):* It would be useful to include data elements that describe the sequelae or impact of the main disease on other diseases. It may also be useful to describe signs and symptoms and experience with treatment beyond the traditional efficacy or effectiveness endpoint.

3. *Why is it important to collect patient experience data? (line 228):* Consider adding "Patients provide context and understanding of the meaningfulness of treatment options".

4. *How can external stakeholders submit patient experience data to the FDA? (Line 264):* The Agency should clarify that all of the links and regulations listed in appendix 2 may not apply to all studies collecting patient experience data. This clarification would be especially helpful for patient groups who would like to submit patient experience data from qualitative or quantitative observational study designs.

5. *How is patient experience data used for regulatory purposes? (Line 290):* It will be important that the Agency clarify mechanisms for communicating collected patient experience data back to patients and health care providers and other relevant

stakeholders. Also please be more specific about mechanisms on how to engage in early interactions with the Agency to support data collection and analysis.

GENERAL CONSIDERATIONS FOR COLLECTING PATIENT EXPERIENCE DATA

1. General Comment (Line 301): While this is an initial guidance meant to lay the foundation for the next three reports, much of the content may be too unfamiliar or complex for non-researchers in the patient advocacy space to understand, but too simplistic to be helpful for researchers. Numerous scientific terms and statistical terms are used throughout the document without being defined, this may make it difficult for a non-researcher to interpret. The target audience and intention of this first guidance should be well explained and reiterated in this document.

2. *Who should provide the patient experience data (Line 412):* While the primary source of patient experience data should come from the patient, the caregiver perspective can be valuable in situations where the patient is simply not able to provide their own perspective. The exact conditions under which the target patient cannot respond and proxy responses from a third party are necessary should be discussed. "CFR - Code of Federal Regulations Title 21" should be mentioned in order to define the ‘patient’.

3. The guidance acknowledges that the health state could influence who the reporter should be, but it doesn't carry over into the sampling frame recommendations.

Determining the Study Design and Research Setting (Line 461)

Sampling Methods and Representativeness (Line 481 and Line 546)

1. This document does a thorough job explaining sampling and representativeness for collecting patient experience data. ISPOR and its membership agree that patient experience research needs to be conducted in a rigorous fashion. Many of our members are patient advocates and while they are highly invested in ensuring that patient experience data is taken into account when planning drug development, they are also less statistically minded when thinking of their representative experience. Patients and their representatives are a constituency that this document is rightly encouraging to be involved in collecting such data. If the Agency truly wants this group to be actively involved, then it should be acknowledged that this guidance may not be well-understood by these types of ‘would-be’ researchers. We recommend that the Agency explicitly acknowledge this discrepancy and perhaps address is it in a health-literate, patient-friendly, less technical document separate from this guidance. This separate document would both encourage patients and advocates, as well as help them understand the limitations of these types of studies.

2. Figure 2 (line 661): It would be helpful to have a real example where the sampling frame doesn’t cover the target population and causes sampling bias.

3. *Sufficient representativeness (line 671):* Patient collected data is often a convenience sample. While it may provide rich patient experience data with the disease and its treatment options, these data would need context on representativeness for interpretation. The Agency could suggest, for example, that the sample characteristics could be compared to patient characteristics from probability samples or epidemiologic studies using a census from a defined population (say all members of a large commercial health plan).

Additional Considerations (Line 663)

1. A distinction should be made between preference studies intended to support benefit/risk and label discussions for a product, and those to gain understanding of patient-relevant endpoints and thus inform clinical trial design. Conducting preference studies in discovery or in pre-competitive situations may dictate the use of different methodologies; the level of rigor in design or sample size may be different than those used later in the development lifecycle. The Agency should try and separate out these different uses of preference data and be specific for each on their demands, level of rigor and statistical robustness, or required need for pre-discussion.

2. *Leveraging Existing Data (Line 705):* Leveraging existing data through different methods could also introduce bias since the various databases were intended for other purposes and could involve unknown confounders in interpreting results. This section would also benefit from a discussion of potential overlap in the data collection efforts.

Qualitative Research Methods (Line 727)

1. There are numerous qualitative analytical approaches that may be suitable when exploring qualitative data. We agree that the steps outlined by the Agency are core to many of the qualitative analytical approaches; however, some greater clarification or recognition that there are other approaches to qualitative analysis would be helpful.

2. Appendix 1 lists Software for Analyzing Quantitative Patient Experience Data, but no software for Qualitative Patient Experience Data (e.g., ATLAS.TI, MAXQDA) is listed - these kinds of software packages have a long tradition in qualitative research and should be included. No mention is made of methods to ensure coding consistency and agreement, nor is any clear idea of how to identify themes provided. This should be addressed.

3. Line 748: Please consider updating the sentence starting on line 748 to something similar to “The FDA acknowledges that there are different approaches to qualitative data analysis depending on the type of data collected. The FDA recommends that stakeholders consider these general steps outlined in Figure 4 when selecting the appropriate qualitative analytical approach for their data”. This would add extra credibility to the analytical section by recognizing that various qualitative approaches available to the researcher have been validated and become established in research, and that these may change depending on the design of the qualitative study. This also

reinforces the idea that the research should make sure that the core steps outlined by the FDA are included.

Mixed Methods (Line 829)

Consistent with current Agency thinking, mixed methods are a key approach to collecting patient experience data. An ISPOR Patient Reported Outcomes Task Force will be submitting a good practices report on this topic in 2018.

Qualitative/Quantitative/Mixed Methods are both observational research (OR) and market research (MR) methodologies, so additional clarity on the differences from the Agency regarding MR versus OR will be helpful to sponsor organizations. Please expand description of, use and examples of mixed methods.

OPERATIONALIZING AND STANDARDIZING DATA COLLECTION AND DATA MANAGEMENT (Line 865)

1. *Locating Patients and Sites (Line 878):* Emphasizing data collection through "sites" misses more current approaches such as online and social media to collect patient experience data. Such approaches may support more representative data by considering geography, disease severity and mobility limitations. Due consideration of bias due to differences between patients who heavily participate in social media and those who do not is important, but can be addressed by use of multiple approaches. Because patient data can be collected through various sources and formats, the Agency should be more explicit regarding the requirements for complying with CDISC standards for Agency submission.

2. *Collecting Data (Line 910):* During data collection, it is useful to collect information about the level of severity and concomitant diseases or symptoms a patient may be experiencing (e.g. chronic versus acute diseases)

3. *Interviews and Focus Groups (Line 932):* These approaches would be qualitative and hence should be stated as such.

4. *Observations (Line 942)*: An addition to this section could include "Observation of individuals in their homes (natural environment) could provide insights into how they adapt to, cope with, or make accommodations for their illnesses that might not be mentioned using other observational techniques."

What are some key considerations when using questionnaires to collect patient experience data? (Line 992)

1. In stated preference methods, experimental designs are often set up so that different respondents see different combinations of questions; this design ensures that respondents consider multiple concepts at once and make trade-offs between them. The

questions are the same in general, but the attributes or attribute/level combinations differ. This is a crucial point to clarify.

2. Consider adding:

    a. "Consider health literacy issues and tailor language and sentence structure accordingly."
    b. "Web-surveys should undergo careful pre-testing or piloting to avoid technical issues and ensure any "skip" patterns are working as planned. Attention to visual quality and usability of the online survey should also be pre-tested."

3. *Social Media and Identifiable Patient Communities (Line 1042):* Social media listening can be used to good effect as long as the researcher is cognizant that other internet users will also add their comments and may not be 'patients' or other relevant parties.

4. Consider a discussion of statistical methods for handling missing data (e.g., imputation, sensitivity analysis, etc.)

CONCLUSION (Line 1160)

Please emphasize in other places in the document, that the Agency encourages early interactions (including relevant patient partners) and obtaining feedback from the relevant review division on appropriate research design and any applicable regulatory requirements.

With limited time during milestone meetings and the Agency's increasing volume of meeting requests, researchers need more clarity on the best mechanisms to request and obtain this feedback. Allocating additional time at milestone meetings may be the most efficient way to support discussions. A specific timeline with specific input /discussions milestones should be outlined as to not delay development. It is also important for Sponsors to understand why FDA accepted or did not accept a particular proposal for collection of patient experience data.

GLOSSARY

Missing terms:

> Outcomes Research: The scientific discipline that evaluates the effect of health care interventions on patient related, if not patient specific, clinical, humanistic, and economic outcomes. Outcomes research is generally based on the conceptual framework that evaluation of treatment alternatives involved the simultaneous assessment of multiple types of outcomes that are disease-related. ('Health Care Cost, Quality, and Outcomes: ISPOR Book of Terms 2003)

Suggested amendments to glossary terms:

Attribute (Line 1341) - the definition is too narrow. Firstly, it may not be a characteristic of a medicinal product. An attribute could also belong to a hypothetical product profile, for instance

to determine which symptoms are of most significance to patients. Similarly, the benefit/risk text would only apply when looking at preferences in relation to a product, whereas in the discovery/pre-competitive phase, preferences may be agnostic of any product.

Caregiver (Line 1361) - the definition of caregiver does not seem to include a child's parent

Clinical Outcome Assessment (Line 1376) - increasingly, digital evidence capture (e.g. through wearable electronic devices, apps, actigraphy) is being employed to capture patient-based evidence, for example to supplement PRO data. It would be good to include this among the possible types of COA.

Patient Engagement (Line 1479) - the definition of patient engagement here does not seem to align with the Introduction of this document. The examples given are much more limited and do not involve patients as partners.

Research Protocol (Line 1578) – this definition refers specifically to a 'clinical research protocol'. Patient preference studies, require a research protocol but may not necessarily be 'clinical research' – consider clarifying.

Social Media (lines 1598-1601) defines such tools as "web-based" tools used for "computer-mediated communication." However, not all such tools are web-based and computer-mediated. We propose the term "virtual platforms" to replace "social media" in the guidance, wherein "virtual platforms" may include "social media." Further, the definition of "social media" should be modified to remove references to "web-based" tools and "computer-mediated communication."

Trade-off (Line 1620) - this can apply to other choice decisions made by patients in a preference study, not solely restricted to attributes of a product.