ISPOR
The professional society for health economics and outcomes research

Improving healthcare decisions

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December 5, 2024

Docket Number: FDA-2015-D-1580-0040

Dear FDA:

ISPOR – the professional society for health economics and outcomes research - is pleased to respond on behalf of its membership to your consultation entitled "Incorporating Voluntary Patient Preference Information over the Total Product Life Cycle."

ISPOR is a scientific and educational society with many of its members engaged in evaluating health technologies, including pharmaceuticals, medical devices, and other interventions. We have a large membership living and working in 110 countries globally, 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, 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.

The response to this consultation was led by the ISPOR Science Office. Comments were solicited from ISPOR's most senior advisory body, the Health Science Policy Council, as well as the ISPOR Institutional Council, Health Preference Research Special Interest Group, and the ISPOR Patient-Centered Special Interest Group. The attached document provides a summary based on their comments. We hope they prove useful.

ISPOR would be happy to answer any questions about our response, to serve as a partner, or to participate in any follow-up consultations on the relevant program items mentioned within the report.

Sincerely,

Robert Abbott
CEO & Executive Director
ISPOR

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Incorporating Voluntary Patient Preference Information over the Total Product Life Cycle

On behalf of the members of ISPOR – the professional society for health economics and outcomes research, please accept our collective comments regarding the FDA draft guidance titled “Incorporating Voluntary Patient Preference Information over the Total Product Life Cycle.” As a multistakeholder organization, ISPOR represents a diverse network of stakeholders, including patient organizations, healthcare professionals, researchers, academicians, and industry representatives. ISPOR is the global leader that pioneered scientific measurement and use of patient preferences through our Good Practice Reports, which are prominently cited in the draft guidance.[1-6]

As a Society committed to furthering sound scientific evidence, we believe that patient preferences should be an integral part of healthcare decision making. ISPOR’s response to this guidance document emphasizes the importance of patient-centered care and meaningful patient engagement in research. ISPOR defines patient engagement in research as "the active, meaningful, and collaborative interaction between patients and researchers across all stages of the research process, where research decision making is guided by patients' contributions as partners, recognizing their specific experiences, values, and expertise."[7] These elements are essential to designing medical products that meaningfully address patient and caregiver needs and preferences. Meaningful input from patients and caregivers throughout the stages of research enhances the quality of research and improves health outcomes. By ensuring that clinical trial results reflect authentic patient experiences, patient preference information (PPI) can support more informed regulatory decisions that align closely with patient and caregiver values.

ISPOR members were engaged in the review of this draft guidance, and this document summarizes the points raised. We identified several opportunities for improvement in the current guidance that could maximize the effective integration of PPI with clinical trial data, specifically in aligning clinical trial endpoints with outcomes that are meaningful to patients and caregivers. Members emphasized the integration of patient input in the early stages of clinical trials and product design; this timely integration of patient preferences and perspectives provides the most significant opportunity. FDA guidance could play a vital role in shaping industry standards and expectations, reinforcing the voices of the patient community. As such, we recommend the FDA revise its guidelines to place greater emphasis on including patient preference data in regulatory submissions as a means to demonstrate that measurement attributes were identified in a patient-centered manner.

ISPOR members also highlighted the need to better define the role of formal and informal caregivers in PPI studies and they recommended expanded discussions and specific examples on integrating care-partner perspectives. Clinical endpoints may not always be high priorities for patients or their caregivers, but their relative importance can be identified using preference data. Ultimately, this approach ensures that the patient perspective is incorporated throughout the research and development processes.

The integration of PPI into clinical trials requires consideration of heterogeneity, representativeness, and statistical methodologies, as patient preferences may potentially vary across subgroups with distinct characteristics.[8] We recommend that the guidance provide strategies for subgroup analyses and methods addressing preference data heterogeneity. We also recommend that the integration of PPI throughout the entire product lifecycle, extending beyond clinical trials and into the post-marketing phase to ensure that patient perspectives continue to inform safety, efficacy, and real-world outcomes as the product is used by a broad patient population.

We advise the FDA to broaden PPI’s scope beyond biologics and drugs to other health technologies. Given the rapid growth of digital health technologies, these tools can further enrich PPI across diverse areas of healthcare innovation. Our recommendations also emphasize the growing use of digital tools for preference

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elicitation such as through mobile devices, including guidance on real-time data collection methods and validation requirements for such digital approaches.

In summary, we recommend the FDA, and other regulatory agencies, make PPI a standard, integral component of clinical trials and health assessments. A more patient-centered approach, along with transparent methodologies, will ensure patient voices are central to decision-making processes in healthcare innovation. We hope these overarching themes provide useful context for our input on enhancing the role of PPI in clinical trial design and regulatory decision making. Please see suggested recommendations from ISPOR members below, organized to align with the specific sections of the draft guidance.

We thank the FDA for considering these recommendations and are available to provide additional and direct scientific input on patient preferences beyond our response to this guidance. For example, if the FDA would be interested in ISPOR identifying one of our member experts to assist with your preference needs, we would be happy to do so. We would also be interested in identifying what gaps FDA feels exist in our good practice reports so that we can work with our members to address them. Should the FDA be interested in working with us in these ways, please contact ISPOR's Chief Science Officer, Laura Pizzi, directly at lpizzi@ispor.org.

We acknowledge ISPOR members Barry Liden, John F. P. Bridges, and Paola Valinotti for their assistance in assembling these comments, as well as ISPOR staff Laura Pizzi, Clarissa Cooblall, Kelly Lenahan, and Sahar Alam.

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Line Specific Comments

I. Introduction

1. Lines 16-22: The FDA may wish to consider adding language that explicitly connects PPI to improving patient-centered care and treatment effectiveness. The current text focuses on regulatory value but could be expanded to include: "This input can be important to consider during FDA's decision making for these devices and helps ensure medical products better meet patient needs."

II. Background

1. Lines 1-14: Several members note that the term "voluntary" may be redundant and potentially undermining, as it may unnecessarily diminish the importance of PPI in regulatory decision-making.
2. Lines 60-94: The guidance's heavy focus on devices raises questions about its applicability to other product types, including combination products and biologics that may involve device components. The FDA may wish to consider:
    a. Clarifying CDER's perspective on PPI submissions and explaining to what extent the guidance applies to drug evaluations
    b. Addressing CBER's role more explicitly, given its co-authorship but limited mention of biologics in the guidance
    c. Providing specific guidance on how PPI considerations might differ across centers and explaining the alignment of this guidance with other FDA guidance documents that reference PPI

III. Scope

1. Lines 96-142: Members note that preference-sensitive situations should include scenarios where patients may choose to forgo treatment when they perceive the risks as worse than their current disease burden. The FDA may wish to consider:
    a. Revising the text around preference-sensitive decisions to explicitly include the option of foregoing treatment when risks are viewed as worse than the condition burden.
    b. Providing guidance on how to appropriately incorporate and analyze opt-out options in preference studies.
    c. Adding a fourth example of preference-sensitive decisions where benefits may not clearly outweigh risks but there is great unmet need for treatment.

IV. Including patient input in FDA decision-making

1. Lines 177-179: Members suggest that the term "care-partners" could be expanded to include both family caregivers and professional caregivers, particularly in cases where patients may be unable to care for themselves or communicate their preferences. FDA may wish to consider:
    a. Clarifying the terminology around care-partners and caregivers to ensure comprehensive coverage of different support roles.
    b. Providing more context about when care-partner or healthcare professional preferences should be considered and addressing how to weigh care-partner preferences against patient preferences when both are available.
2. Lines 226-244: Members request clearer differentiation between PPI and PROs, and better articulation of care-partner roles. FDA may wish to consider: "Providing specific guidance on when and how to incorporate care-partner perspectives and adding examples of successful integration of patient and care-partner inputs."
3. Lines 235-244: The translation of clinical endpoints into preference attributes requires careful consideration to ensure patients can make meaningful trade-off decisions. At present, Lines 235-244 provide limited guidance on this critical process. Without clearer direction, sponsors may struggle to create preference studies that meaningfully capture patient perspectives on clinical outcomes and

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associated trade-offs, particularly for complex endpoints or biomarkers.

4. Consider expanding Line 418 to read: "Clinical endpoints and preference attributes should demonstrate clear alignment. When using surrogate endpoints or technical measurements, sponsors must document the relationship between clinical endpoints and patient-relevant outcomes."
5. Additionally, FDA may wish to consider adding guidance after Line 428 addressing:
    a. Methods for translating technical clinical endpoints into patient-meaningful terms and approaches for validating that patients can meaningfully evaluate the endpoints.
    b. Requirements for documenting how clinical data informed attribute definitions and processes for addressing any disconnects between clinical significance and patient importance.

V. Recommendations and Practical Considerations for Patient Preference Studies

1. FDA may wish to consider revising Line 413 to read: "Patient-centered approaches actively engage patients as research partners throughout the study process, ensuring the research questions, methods, and outcomes reflect patient priorities and experiences."
2. Lines 413-417: FDA may wish to consider:
    a. Encouraging patient engagement in study design and protocol development and expanding guidance on ensuring diversity in patient input during development stages
    b. Providing guidance on incorporating patient input in attribute selection and study design and recommending approaches for engaging patients as reviewers in the FDA review process
    c. Addressing approaches for maintaining patient engagement throughout the research process.
3. Line 415: Replace "sponsors may engage with patients" with "sponsors should engage with patients"
4. Line 416: After "…well-informed about the benefits and risks", add "through appropriate education methods that balance comprehensive information with cognitive burden. 'Well-informed' means participants can demonstrate understanding of key benefits and risks relevant to preference decisions, as verified through appropriate comprehension assessment methods."
5. Line 429: Replace "Various types of patient preference studies exist" with "Selection of appropriate patient preference methods should be guided by study objectives, population characteristics, and decision context. Key considerations include:"
6. Add after Line 429: "a) Complexity of benefit-risk trade-offs; b) Characteristics of the target population; c) Type of preference information needed; d) Resource and practical constraints; e) Intended use of preference data"
7. Lines 440-445:
    a. Add guidance around line 440 on when preference studies should be conducted relative to clinical trials.
    b. Provide recommendations on using the same versus different populations for clinical trials and preference studies and including considerations for updating preference information as clinical evidence evolves.
8. Line 449: Consider adding guidance after line 449 about appropriate sample sizes for different methodological approaches such as, "including recommendations for handling populations where large samples are difficult to obtain and providing guidance on statistical power considerations for subgroup analyses."
9. Expanding lines 465-466 to provide specific guidance on:
    a. Minimum sample size requirements for different study types
    b. Handling situations where large samples are difficult to obtain
    c. Methods for assessing sample representativeness
    d. Adding guidance around line 468 on balancing subgroup representation versus population proportions
    e. Including recommendations for documenting and justifying sample size decisions when working with rare diseases or hard-to-reach populations
10. FDA may wish to consider revising Line 521 to read: "Sponsors should conduct qualitative research

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with patients to inform attribute selection and study design. While FDA consultation is valuable, it should complement, not replace, direct patient input."

11. Add after Line 525: "Documentation of patient engagement in study design should include:
    a. Methods used to gather patient input
    b. Number and diversity of patients engaged
    c. How patient input influenced attribute selection
    d. Changes made based on patient feedback
    e. Rationale for accepting or rejecting patient suggestions"
12. Lines 514-589: FDA may wish to consider revising Section V.F to:
    a. Strengthen language around the requirement for patient input in attribute selection, rather than presenting it as optional
    b. Clarify that discussions with FDA should complement, not replace, patient input in attribute development
    c. Emphasize that qualitative research with patients should inform attribute selection and definition

VIII. Inclusion of Patient Preference Information in Decision Summaries and Device Labeling

1. FDA may wish to consider:
    a. Adding around line 827 a mock example demonstrating how PPI studies supporting benefit-risk assessment would be included in product labeling
    b. Expanding guidance on:
        i. How to present benefit-risk tradeoff preferences in labeling
        ii. Methods for communicating preference heterogeneity
        iii. Approaches for updating labeling as preferences evolve

X. Appendix A and XI. Appendix B

1. 1030-1140 (Appendix B): FDA may wish to consider adding before reference to Appendix B: "Emerging Methods Assessment When proposing newer preference elicitation approaches, sponsors should provide: a) Theoretical foundation b) Validation evidence c) Advantages over established methods d) Potential limitations e) Special considerations for implementation"
2. Add guidance on referencing Appendix B: "While Appendix B provides an overview of established methods, sponsors considering emerging approaches should document:
    a. Relationship to established methods
    b. Evidence supporting scientific validity
    c. Special considerations for implementation
    d. Additional validation requirements"
3. Lines 1109 –1112: FDA may wish to consider:
    a. Addressing the role of digital health tools in preference elicitation
    b. Providing guidance on real-time preference data collection methods
    c. Discussing validation requirements for novel digital approaches
    d. Outlining considerations for integrating digital tools with traditional preference assessment methods