NATIONAL HEALTH COUNCIL

December 5, 2024

The Honorable Robert M. Califf, MD
Commissioner
U.S. Food and Drug Administration
5630 Fishers Lane
Rockville, MD 20852

RE: Incorporating Voluntary Patient Preference Information Over the Total Product Life Cycle; Guidance for Industry, Food and Drug Administration Staff and Other Interested Parties [Docket No. FDA-2015-D-1580]

Submitted electronically via regulations.gov

Dear Commissioner Califf,

The National Health Council (NHC) appreciates the opportunity to provide comments on the FDA's draft guidance *Incorporating Voluntary Patient Preference Information Over the Total Product Life Cycle*.

Created by and for patient organizations over 100 years ago, the NHC brings diverse organizations together to forge consensus and drive patient-centered health policy. We promote increased access to affordable, high-value, equitable, and sustainable health care. Made up of more than 170 national health-related organizations and businesses, the NHC's core membership includes the nation's leading patient organizations. Other members include health-related associations and nonprofit organizations including the provider, research, and family caregiver communities; and businesses and organizations representing biopharmaceuticals, devices, diagnostics, generics, and payers.

Recommendations to Enhance the Draft Guidance

The NHC values the FDA's ongoing commitment to patient-centered regulatory practices. The draft guidance significantly enhances the existing framework by outlining how Patient Preference Information (PPI) can inform benefit-risk assessments across the total product life cycle (TPLC). While the current guidance focuses primarily on the pre-market phase, the NHC believes it is important to also emphasize that patient input throughout the entire product life cycle is essential. Continued patient feedback post-market is critical for ensuring that medical products remain aligned with patients' needs and priorities as they evolve over time. We especially applaud the inclusion of diverse hypothetical examples and the emphasis on early engagement between sponsors and FDA staff, which foster alignment on study design and objectives. These steps will help ensure that PPI is thoughtfully integrated into regulatory processes to reflect patients' voices and their ongoing perspectives as products evolve over time. Please find

additional recommendations below, which are intended to further strengthen the draft guidance.

Enhancing Representativeness and Diversity in PPI Studies

The NHC appreciates the FDA's emphasis on the importance of representativeness in PPI studies to ensure that results are generalizable across diverse patient populations. Representativeness is essential for equitable health care, ensuring that regulatory decisions reflect the preferences and needs of all patient populations, particularly underrepresented or marginalized groups. To strengthen the draft guidance, the FDA should outline additional strategies to address persistent challenges in achieving diverse participation and ensuring inclusivity in study designs.[1]

Recruitment of underrepresented populations, such as racial and ethnic minorities, individuals with disabilities, and those from rural areas, requires a multifaceted approach.[2] Barriers to participation, including geographic isolation, economic constraints, and linguistic differences, often exclude these groups from research, limiting the generalizability of study results.[3] One effective strategy involves leveraging patient organizations that have built trust within specific communities. These organizations act as bridges between researchers and patients, fostering engagement and addressing concerns specific to their constituencies.[4] Additionally, employing remote data collection tools, such as telehealth platforms or mobile applications, can help overcome geographic and logistical barriers that prevent individuals in underserved areas from participating.[5] Remote tools also offer flexibility for participants who may face challenges attending in-person sessions, such as those with disabilities or caregiving responsibilities. Moreover, providing culturally sensitive study materials tailored to the

[1] National Health Council. Roadmap and Rubric for Enhancing Representativeness in Patient Engagement Activities. Published December 2019. https://nationalhealthcouncil.org/wp-content/uploads/2019/12/Oehrlein_HTAi_Representativeness_final.pdf.

[2] Hatch, Sarah, Jane Fitzgibbon, Andrew J. Tonks, and Laura Forty. "Diversity in Patient and Public Involvement in Healthcare Research and Education—Realizing the Potential." Health Expectations: An International Journal of Public Participation in Health Care and Health Policy 27, no. 1 (2024): e13896. https://doi.org/10.1111/hex.13896.

[3] George, Sheba, Ninez Ponce Duran, and Keith C. Norris. "A Systematic Review of Barriers and Facilitators to Minority Research Participation among African Americans, Latinos, Asian Americans, and Pacific Islanders." American Journal of Public Health 104, no. 2 (2014): e16–e31. https://doi.org/10.2105/AJPH.2013.301706.

[4] National Health Council. *Summary of Resources for NHC Health Literacy Training*. Published October 2021. https://nationalhealthcouncil.org/wp-content/uploads/2021/10/Summary-Resources-for-NHC-Health-Literacy-Training-3.pdf.

[5] McCaffery, Kirsten J., Stacey K. Smith, and Michael Wolf. "The Challenge of Shared Decision Making among Patients with Lower Literacy: A Framework for Research and Development." Medical Decision Making 33, no. 6 (2013): 724–731. https://doi.org/10.1177/0272989X09342279.

linguistic and cultural backgrounds of potential participants fosters trust and improves understanding, making it more likely for diverse individuals to engage with the study.[6,7]

Inclusivity in PPI studies also requires deliberate consideration of health literacy and numeracy levels among participants. Studies must be designed to ensure that participants, regardless of their educational background, can comprehend the information provided and make informed decisions about their involvement. Providing materials in plain language is a critical first step, as complex or technical jargon can alienate participants and compromise the quality of the data collected.[8] Incorporating visual aids, such as diagrams or infographics, further enhances comprehension by presenting information in accessible, non-textual formats.[9] These tools are particularly useful for individuals who struggle with textual or numerical information. Testing study materials for cultural appropriateness through pre-testing with target populations allows researchers to identify and address potential biases or misunderstandings.[10] Iterative refinement ensures that the materials resonate with diverse audiences and accurately convey the study's objectives.[11] Integrating health literacy considerations into patient decision aids improves understanding and participation among individuals with limited literacy skills.[12]

Research has shown that inclusive approaches to recruitment and study design significantly improve diversity and representativeness in health research. Participation among racial and ethnic minorities is increased by community engagement strategies

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[6] Yancey, Antronette K., Alexander N. Ortega, and Shiriki K. Kumanyika. "Effective Recruitment and Retention of Minority Research Participants." Annual Review of Public Health 27 (2006): 1–28. https://doi.org/10.1146/annurev.publhealth.27.021405.102113.

[7] DeWalt, Darren A., Leigh F. Callahan, Victoria H. Hawk, Kimberly A. Broucksou, Ashley Hink, Rima Rudd, and Cindy Brach. Health Literacy Universal Precautions Toolkit. Rockville, MD: Agency for Healthcare Research and Quality, 2010. https://www.ahrq.gov.

[8] Benz, Heather L., Ting-Hsuan (Joyce) Lee, Jui-Hua Tsai, John F. P. Bridges, Sara Eggers, Megan Moncur, Fadia T. Shaya, Ira Shoulson, Erica S. Spatz, Leslie Wilson, and Anindita Saha. "Advancing the Use of Patient Preference Information as Scientific Evidence in Medical Product Evaluation: A Summary Report of the Patient Preference Workshop." *The Patient: Patient-Centered Outcomes Research* 12, no. 5 (2019): 553–557. https://doi.org/10.1007/s40271-019-00396-5.

[9] Sudore, Rebecca L., and Dean Schillinger. "Interventions to Improve Care for Patients with Limited Health Literacy." Journal of Clinical Outcomes Management 16, no. 1 (2009): 20–29. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2799039/.

[10] Sheridan, Stacey L., David J. Halpern, Anthony J. Viera, Nancy D. Berkman, Katrina E. Donahue, and Karen Crotty. "Interventions for Individuals with Low Health Literacy: A Systematic Review." *Journal of Health Communication* 16, Suppl. 3 (2011): 30–54. https://doi.org/10.1080/10810730.2011.604391.

[11] National Health Council. Guide to Patient Engagement in Health Care Research. Published June 2020. https://nationalhealthcouncil.org/wp-content/uploads/2020/06/NHC_Guide_Research_Engagement.pdf.

[12] Berkman, Nancy D., Stacey L. Sheridan, Katrina E. Donahue, David J. Halpern, and Karen Crotty. "Low Health Literacy and Health Outcomes: An Updated Systematic Review." *Annals of Internal Medicine* 155, no. 2 (2011): 97–107. https://doi.org/10.7326/0003-4819-155-2-201107190-00005.

that foster trust and addressspecific barriers to involvement.[13] Similarly, aligning study materials with the cultural and linguistic needs of participants ensures that information is accessible and meaningful, facilitating broader participation.[14]

The design and execution of PPI studies that truly reflect the diversity of the patient populations affected by regulatory decisions can be encouraged by the FDA incorporating these strategies into the guidance. This focus on inclusivity will not only enhance the validity of PPI studies but also contribute to more equitable health care outcomes by ensuring that all voices are represented in the decision-making process.

Strengthening Clarity on the Role of PPI in Decision-Making

The NHC appreciates the FDA's emphasis on integrating PPI into benefit-risk assessments and its commitment to advancing patient-centered regulatory practices. However, the guidance would benefit from greater detail on how PPI complements other forms of evidence and is systematically incorporated into regulatory decision-making.

One critical area for enhancement is transparency regarding how PPI findings will be weighed alongside clinical trial data, real-world evidence, and health care professional input. While clinical data often serve as the cornerstone of regulatory decisions, PPI provides unique insights into patient priorities that may not be captured through traditional endpoints. For example, PPI can highlight patient tolerance for risks associated with high-stakes devices or preferences for specific tradeoffs in treatment outcomes. Real-world case studies demonstrating how PPI has influenced decisions, such as targeted approvals or label modifications, would clarify its practical utility. A notable example is the role of PPI in the evaluation of obesity devices, where patient perspectives on procedural risks informed regulatory outcomes. Such examples can provide a clearer picture of how PPI complements and strengthens existing evidence bases.[15]

To better quantify these preferences, research has shown that methodologies such as discrete choice experiments and conjoint analysis can be particularly useful. These techniques allow for the systematic measurement of patient tradeoffs, providing regulators with a more nuanced understanding of benefit-risk profiles. By applying these approaches, PPI can fill in gaps left by traditional clinical data and offer a more complete picture of what patients value in treatment decisions.[16]

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[13] Odedina, Folakemi T., Mark L. Wieland, Kim Barbel-Johnson, and Jennifer M. Crook. "Community Engagement Strategies for Underrepresented Racial and Ethnic Populations." Mayo Clinic Proceedings 99, no. 1 (2024): 159–171. https://doi.org/10.1016/j.mayocp.2023.07.015.

[14] National Health Council. Health Equity and Patient Engagement Framework. Published February 2022. https://nationalhealthcouncil.org/wp-content/uploads/2022/02/NHC-Health-Equity-Framework.pdf.

[15] Benz et al., "Advancing the Use of Patient Preference Information as Scientific Evidence in Medical Product Evaluation: A Summary Report of the Patient Preference Workshop."

[16] Bridges, John F. P., A. Brett Hauber, Deborah Marshall, Andrew Lloyd, Lisa A. Prosser, Dean A. Regier, F. Reed Johnson, and Josephine Mauskopf. "Conjoint Analysis Applications in Health—a Checklist: A Report of the ISPOR Good Research Practices for Conjoint Analysis Task Force." *Value in Health* 14, no. 4 (2011): 403–413. https://doi.org/10.1016/j.jval.2010.11.013

While understanding patient preferences is crucial to benefit-risk assessment, it is equally important to consider how such preferences may vary across different subgroups, and how they may evolve over time. For example, newly diagnosed patients and their families often prioritize different treatment goals than those with longer-term experience living with a disease. Early on, families may focus more on immediate disease management or comfort, while over time, their preferences may shift towards considering disease-modifying treatments as they become more familiar with the disease's progression and its impact on quality of life. The guidance should clarify how to reconcile conflicting patient preferences across subgroups within a unified decision framework, recognizing that these preferences can change as patients gain more experience with their condition. Variability in patient preferences—shaped by factors such as demographics, disease severity, and duration of living with the disease—can complicate regulatory evaluations. Subgroup-specific analyses are essential for capturing this heterogeneity, but it is equally important to articulate how these findings will inform decisions without disproportionately favoring one group over another. Techniques such as weighted modeling or conditional approvals for specific subpopulations could be explored as potential solutions to address conflicting preferences. Expanding on these mechanisms would enhance clarity and build confidence among stakeholders regarding the robustness of PPI integration.

Providing a transparent decision rubric that outlines how PPI is balanced against other forms of evidence would further strengthen the guidance. A standardized framework could score PPI based on its methodological rigor, relevance to regulatory questions, and alignment with clinical and real-world evidence. This approach would ensure consistency in how PPI is evaluated and applied. For instance, the FDA's benefit-risk framework could include explicit criteria for incorporating PPI, such as the robustness of the study design or the degree to which preferences align with clinical outcomes.[17]

In addition to its role in pre-market decisions, PPI can be valuable in post-market activities, including the formulation and communication of recall notices. Recalls are often challenging for patients, who may not be aware of them or may find recall notices difficult to decipher. Incorporating patient perspectives can enhance the clarity of these communications, address patients' concerns, and guide them in understanding how to proceed, particularly by involving patients in developing more understandable recall notices and follow-up procedures.

By addressing these areas, the FDA can enhance stakeholders' understanding of PPI's role in regulatory decisions, ensuring that it is integrated meaningfully into a comprehensive and transparent framework.

Incorporating PPI into Public Decision Summaries and Labeling

Incorporating PPI into public decision summaries and device labeling is essential for enhancing transparency and ensuring that medical devices align with patient needs and values. However, the current guidance could provide more detailed instructions on effectively integrating PPI to make findings accessible and actionable for both patients

[17] Berkman et al., "Low Health Literacy and Health Outcomes: An Updated Systematic Review."

and health care providers.[18,19] Including plain language summaries of PPI findings in regulatory submissions, using patient-friendly language and visuals such as icon arrays or risk-benefit diagrams that can make complex data more understandable, and visual aids are particularly effective in improving comprehension among individuals with limited health literacy.[20]

Specialized patient labeling should describe patient preferences for specific benefits and risks, tailored to the population most likely to use the device. Including examples of effective labeling practices, such as incorporating patient testimonials or case studies, helps contextualize the information for potential users.[21] Standardizing the inclusion of PPI in decision summaries, including 510(k) submissions, ensures consistent consideration of patient voices across devices and regulatory pathways, particularly for products involving complex benefit-risk tradeoffs.[22]

Implementing these recommendations ensures that PPI findings are not only integrated into regulatory processes but also presented in ways that are meaningful to patients and health care providers. Such an approach centers patient preferences in decision-making and fosters equitable health care outcomes.

Expanding Guidance on Study Design and Methodology

The NHC appreciates the FDA's detailed guidance on designing PPI studies and recognizes its potential to advance patient-centered regulatory practices. However, further elaboration is necessary to ensure that PPI studies are robust, fit-for-purpose, and tailored to diverse regulatory and clinical contexts.

A comprehensive decision framework would help sponsors select between qualitative, quantitative, or mixed-method approaches based on their research objectives. Qualitative methods, such as focus groups or in-depth interviews, are particularly useful in exploratory stages to identify key attributes and outcomes that matter to patients. In contrast, quantitative methods like discrete choice experiments or conjoint analysis are better suited for evaluating tradeoffs between risks and benefits, especially when

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[18] U.S. Food and Drug Administration. *Patient Preference Information (PPI) in Medical Device Decision Making.* Accessed November 18, 2024. https://www.fda.gov/about-fda/division-patient-centered-development/patient-preference-information-ppi-medical-device-decision-making.

[19] Ho, Martin P., Juan Marcos Gonzalez, Herbert P. Lerner, Carolyn Y. Neuland, Joyce M. Whang, Michelle McMurry-Heath, A. Brett Hauber, and Telba Irony. "Incorporating Patient-Preference Evidence into Regulatory Decision Making." *Surgical Endoscopy* 29, no. 10 (2015): 2984–93. https://doi.org/10.1007/s00464-014-4044-2.

[20] Galmarini, Elisa, Laura Marciano, and Peter Johannes Schulz. "The Effectiveness of Visual-Based Interventions on Health Literacy in Health Care: A Systematic Review and Meta-Analysis." *BMC Health Services Research* 24 (2024): 718. https://doi.org/10.1186/s12913-024-11138-1.

[21] Ibid.

[22] U.S. Food and Drug Administration. *Patient Preference Information (PPI) in Medical Device Decision Making.* Accessed November 18, 2024. https://www.fda.gov/about-fda/division-patient-centered-development/patient-preference-information-ppi-medical-device-decision-making.

detailed statistical assessments are required. Mixed-method approaches can offer the advantages of both, allowing sponsors to explore nuanced patient perspectives qualitatively and validate findings quantitatively. By including a decision framework, the FDA can provide clarity on how to align study design with regulatory goals and patient needs.[23]

The draft guidance should emphasize the critical role of iterative pre-testing in ensuring the reliability and validity of PPI studies. Pre-testing study materials, including surveys and questionnaires, with diverse patient samples helps identify potential biases, comprehension issues, and cognitive overload that could compromise data quality. For instance, pre-tests can reveal if survey questions are framed in ways that unintentionally lead participants toward particular responses. Specific recommendations for pre-testing protocols—such as conducting cognitive interviews, pilot studies, or using think-aloud methods—would further enhance study quality. Pre-testing also ensures accessibility by identifying barriers faced by populations with limited health literacy or numeracy skills.[24]

The draft guidance should include a discussion on advanced statistical techniques that can enhance the robustness of PPI studies. Bayesian modeling and latent class analysis, for instance, are powerful tools for capturing variability in patient preferences and identifying distinct subgroups within the population. These techniques can provide nuanced insights into heterogeneous patient priorities, which are particularly valuable when evaluating preference-sensitive decisions involving complex benefit-risk tradeoffs. Bayesian models can also incorporate prior data, enabling sponsors to optimize study designs and improve decision-making efficiency. Integrating these methodologies into PPI studies would enable sponsors to generate data that are both scientifically rigorous and actionable for regulatory purposes.[25]

By expanding the guidance on study design and methodology to include decision frameworks, iterative pre-testing protocols, and advanced statistical techniques, the FDA can provide sponsors with the tools to develop robust, patient-centered PPI studies. These enhancements will improve the reliability, accessibility, and regulatory utility of PPI, ultimately fostering better alignment between medical device evaluations and patient needs.

Specific Considerations for Pediatric and Caregiver-Informed PPI

The NHC commends the FDA for incorporating a pediatric-specific example in the draft guidance and recognizes the importance of addressing the unique considerations of pediatric and caregiver-informed PPI. However, additional clarity and recommendations are needed to ensure PPI studies accurately reflect the complexities of pediatric care and decision-making.

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[23] Bridges et al., "Conjoint Analysis Applications in Health—a Checklist: A Report of the ISPOR Good Research Practices for Conjoint Analysis Task Force."

[24] DeWalt et al., Health Literacy Universal Precautions Toolkit.

[25] Ho et al., "Incorporating Patient-Preference Evidence into Regulatory Decision Making.".

Caregivers play a pivotal role in health care decisions for pediatric and cognitively impaired populations. Their perspectives are essential in understanding the preferences and tradeoffs that impact treatment choices. The guidance should explicitly address methodologies for capturing caregiver input in PPI studies, such as using conjoint analysis or discrete choice experiments that include both caregivers and patients. For instance, studies could present scenarios that explore how caregivers weigh the benefits of a treatment against its risks or how they prioritize factors like ease of use or cost. This dual-input approach would provide a more comprehensive understanding of preferences and ensure that caregiver perspectives are adequately represented in regulatory decision-making.[26]

When designing PPI studies involving pediatric patients, ethical considerations must guide the inclusion of children's preferences. The FDA should provide detailed recommendations on how sponsors can ethically and effectively engage children in PPI studies. For example, age-appropriate surveys, gamified tools, or visual decision aids can be employed to elicit meaningful input from younger participants while respecting their cognitive abilities and developmental stages. Additionally, the guidance should address the role of parental consent and how it intersects with a child's ability to provide assent. Ethical frameworks that consider both parental authority and the child's evolving autonomy would help sponsors navigate these complex dynamics.[27]

PPI studies for pediatric applications may reveal differing preferences between children and their caregivers. For example, caregivers may prioritize long-term health outcomes, while children may focus on immediate comfort or reduced procedural burden. While some literature suggests that pediatric patients and caregivers may have differing preferences, particularly when it comes to balancing long-term outcomes with immediate comfort, we acknowledge that this dynamic may not always be present across all patient populations. In some rare disease contexts, caregivers may prioritize comfort and the reduction of procedural burden more than the pediatric patients themselves, reflecting the broader understanding of long-term treatment impacts. Further research is needed to better understand these dynamics, and we encourage the FDA to review the available literature on the subject. The guidance should outline strategies for sponsors to capture and address these differing preferences within a unified benefit-risk framework. Analytical techniques, such as multi-attribute decision analysis or latent class analysis, could be employed to explore how various priorities influence decision-making. By addressing these dynamics transparently, PPI studies can more effectively inform regulatory decisions that consider both caregiver and pediatric patient needs.[28]

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[26] Crossnohere, Nancy L., Rebecca Fischer, Emily Vroom, Pat Furlong, and John F.P. Bridges. "A Comparison of Caregiver and Patient Preferences for Treating Duchenne Muscular Dystrophy." *The Patient: Patient-Centered Outcomes Research* 15, no. 5 (2022): 577–588. https://doi.org/10.1007/s40271-022-00574-y.

[27] Ott, Marilyn A., Francis P. Crawley, Xavier Sáez-Llorens, Samuel Owusu-Agyei, Diane Neubauer, Gregory Dubin, Tamara Poplazarova, Nicholas Begg, and Sandra L. Rosenthal. "Ethical Considerations for the Participation of Children of Minor Parents in Clinical Trials." *Paediatric Drugs* 20, no. 3 (2018): 215–222. https://doi.org/10.1007/s40272-017-0280-y.

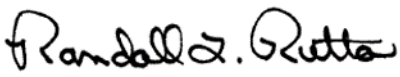
The guidance should emphasize the importance of rigorous study designs tailored to pediatric populations. Recommendations should include guidance on sample size considerations for studies involving rare pediatric conditions, as well as strategies for recruiting diverse caregiver and patient populations. Ensuring that PPI studies capture a representative sample of the intended population is particularly critical in pediatric research, where small sample sizes and heterogeneity often pose challenges. Iterative pre-testing of study materials with both caregivers and children can also help refine methodologies and enhance study validity.

By addressing the unique dynamics of caregiver input, the ethical inclusion of children's preferences, and strategies to balance conflicting priorities, the FDA can strengthen its guidance on PPI studies for pediatric applications. These recommendations will ensure that PPI studies are comprehensive, methodologically rigorous, and reflective of the perspectives of both caregivers and pediatric patients.

Conclusion

The NHC appreciates the FDA's leadership in advancing patient-centered regulatory practices. By incorporating the recommendations above, the FDA can further strengthen the draft guidance, ensuring that PPI meaningfully informs decision-making and improves outcomes for diverse patient populations. We welcome continued collaboration with the FDA to promote the integration of patient perspectives across the TPLC. Please do not hesitate to contact Jennifer Dexter, Vice President of Policy and Government Affairs, at jdexter@nhcouncil.org if you or your staff would like to discuss these comments in greater detail.

Sincerely,



Randall L. Rutta
Chief Executive Officer

[28] Zhou, Min, William M. Thayer, and John F.P. Bridges. "Using Latent Class Analysis to Model Preference Heterogeneity in Health: A Systematic Review." *PharmacoEconomics* 36 (2018): 175–187. https://doi.org/10.1007/s40273-017-0575-4.