

Patient-reported outcomes and patient preference information in regulatory decision making



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This article discusses the patient-focused trends in collecting patient experience data (PED), such as patient-reported outcomes (PROs) and patient preference information (PPI), for use in regulatory decision making and drug development. The authors cover current programs initiated by the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) and discuss how the agencies and sponsors can collaborate to elevate the role of PROs and PPI in informing regulatory decisions. Special attention is placed on the challenges and opportunities for using PED, in particular: PROs in oncology, where PED have historically rarely been collected and even more rarely used; and critical PPI study considerations that have the poten-

tial to advance the use of PPI in multiple therapy areas. The authors conclude there is an increasing recognition of the value in patients' unique insights into living with a disease and the importance of incorporating their perspectives into regulatory decision making. However, they also stress it is critical to continue the strong productive collaboration with regulators and use of forthcoming regulatory guidance to ensure that the collection methods and analyses of PED are fit for their intended purpose and that the resulting data are of high quality, so that they can reliably inform regulatory reviews.

Introduction

There is an increasing recognition of patients' unique expertise and the importance of incorporating their perspectives both in drug development and clinical care. Accordingly, patients are at the center of regulatory affairs and all of drug development. Patient-focused drug development (PFDD) begins with identifying what matters most to patients and continues with addressing the need to develop truly patient-centric PROs. In addition, PPI, capturing patients' perspectives on potential treatments and their willingness to accept treatment risks to achieve treatment outcomes that matter to them provides additional insight into the acceptability of treatments to patients. Using PED, including PROs and PPI, in regulatory decision making requires quality

data, as well as robust, fit-for-purpose methodologies and flawless execution.

While there has been great progress to advance PFDD,¹⁻³ there is a need to sustain the momentum. Specifically, there is a need for increased early engagement with regulators and increased partnering to ensure the PED generated is valid and reliable, thus fit for regulatory decision making. It is critical that, once the fitness criteria are met, the resulting high-quality PED is actually considered during the regulatory assessment. It should also be highlighted that appropriately designed studies and collection of PED can inform sponsor decisions (e.g., study design) and other regulatory decisions (e.g., postapproval decisions) throughout a medicine's lifecycle. To realize the full value of PED, sponsors and regulators must continue collaborating so that the methodologies for collecting and analyzing PED can be developed efficiently (e.g., by sharing learnings) and therefore used more readily in global development programs. In addition, it will be important that emerging digital innovations for collecting and communicating PROs, PPI, and other types of patient experience data are also incorporated into the PFDD toolkit.

Patient-reported outcomes (PROs) are outcomes that are directly reported by the patient and considered without interpretation of the patient's response by a clinician or anyone else. PROs refer to the patient's health, quality of life, or functional status and may be measured in real and absolute terms, such as severity of pain.

Patient preference information and PROs are both powerful mechanisms that increase the voice of the patient in regulatory decision making and the FDA, EMA, and sponsors are working together to further advance the science of patient-focused drug development.

What are PROs?

Patient-reported outcomes are outcomes that are directly reported by the patient and considered without interpretation of the patient's response by a clinician or anyone else. PROs refer to the patient's health, quality of life, or functional status and may be measured in real and absolute terms, such as severity of pain. PROs can also be used to report changes from a previous measure, such as new onset of nausea.

The pharmaceutical industry has recognized the importance of considering PROs along with their focus on improving health-related quality of life for enhancing drug development, guiding regulatory decisions, and supporting shared decision making.

However, there are challenges that emerge with the use of PROs. To validate PRO measures, there must be an appropriately sized representative patient population – and finding that is often rare at the initial stages of clinical development. Also, one may expect variability and subjectivity of patient experience and perception. One must also take care to not ask too many questions because complicated and weighty surveys can lead to response fatigue. It is also possible that disease-specific PRO measures reflect a patient's health care journey but may lack validation common among less specific, generic PROs.

PROs in oncology and clinical outcome assessments

Incorporating PROs into oncology trials can face barriers, both multiple and real. First, developing PRO measures that satisfy US Food and Drug Administration (FDA) standards can take years. Second, oncology drug development programs are accelerated programs with compressed timelines to accelerate their path to market. Accelerated timelines may not easily accommodate the development and use of PROs.

Other challenges to integrating PRO measures across multinational clinical trials in oncology include small trial population sizes and the fact that patients are often very sick or terminally ill. However, such challenges may be overcome by using a clinical outcome assessment (COA), which measures, describes, or reflects how a patient feels, functions, or survives. The types of COAs include:

- Patient-reported outcome (PRO) measures
- Observer-reported outcome (ObsRO) measures
- Clinician-reported outcome (ClinRO) measures
- Performance outcome (PerfO) measures

The FDA's Center for Drug Evaluation and Research (CDER) has two pathways for reviewing COAs, through the CDER COA Qualification Program or under an individual drug development program. FDA COA qualification depends on whether the agency finds the COA well defined and reliable.

Historically, PROs were typically absent in oncology, and when included, they were rarely published. For example, a review of 160 oncology trials from 2014-2017 with published results revealed that 61 studies failed to include their PRO findings in any publication, whereas 99 included PROs, but with inadequate reporting standards as set by FDA's CONSORT PRO Extension checklist.⁴ Half of the trials publishing PRO results in a secondary publication took more than 4 years to be reported following trial closure and 36% took 5-8 years to report PROs.

PRO measures are also historically absent in US oncology labels. A review of product labels for PROs in the US from 2006-2010 found that, of 116 products identified, 16 were reviewed by the FDA's oncology division and none was granted any PRO claim in the label.⁵ Of the remaining 100 products, 28 (24%) were granted PRO claims, of which 24 (86%) were for symptoms and 9 (38%) were pain related.

The FDA supports development of qualified PRO measurements through contributions and participation in the Patient-Reported Outcomes Consortium, a col-

laborative PRO effort between FDA, industry, and the Critical Path Institute.⁶ In 2009, the FDA released a guidance document for specifying types of evidence and documentation required for PRO measures to support regulatory approval and labeling claims.⁷

The recent focus on PFDD is improving the PRO landscape in oncology. In 2014, an expert panel made key recommendations regarding the promotion of oncology-specific PROs and existing PRO measures while emphasizing training programs for those conducting trials who were interested in PRO assessment. The FDA and EMA are working together with industry to increase the use of PROs in oncology trials, which should result in more PROs in oncology product labels.

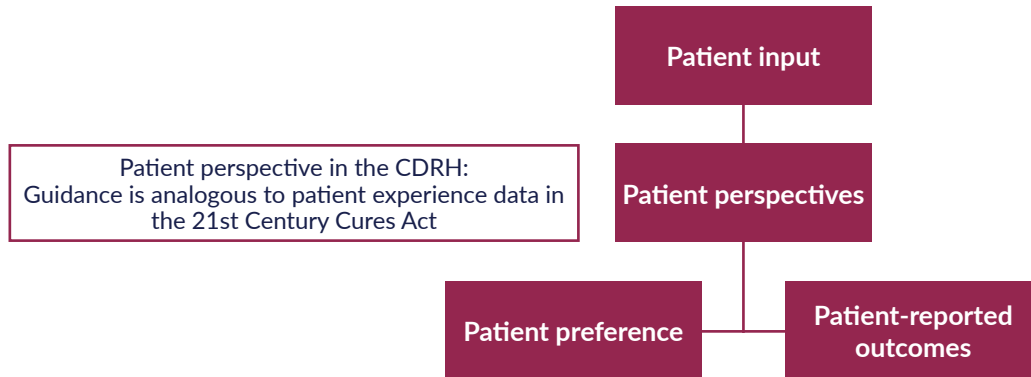
In 2016, the EMA's Committee for Medicinal Products for Human Use adopted Appendix 2 of the agency's guideline on the evaluation of anticancer medicinal products, which is focused on the use of PRO measures in oncology studies.⁸ In 2021, the FDA released guidance on the use of core PROs in cancer clinical trials.⁹ In addition, the agency has a webpage dedicated to the FDA pilot grant program for standard core clinical outcome assessments (COA) and their related endpoints,¹⁰ and another that lists qualified COAs in oncology and other areas.¹¹

PROs are becoming increasingly important in drug development, but they must be carefully defined so that they capture information that is important to patients. In addition, the information must also be measured accurately so that it is comparable with other measurements. Both the FDA and EMA have ongoing initiatives for improving the quality of PROs for use in approvals and in labels.

Patient preference information: The path forward

Studies generating PPI have been used recently to quantify the importance that patients place on the benefits of treatment and their willingness to accept treatment-related risks to achieve those benefits. The FDA's prevailing definition of patient preferences is that they are "qualitative or quantitative assessments of the relative desirability

Figure 1. Patient preferences and experience: Guidance on patient input



CDRH, Center for Devices and Radiological Health

Source: DiSantostefano R, et al C. Characterizing patient experience data in medical product development: what is it, what is expected, and how can you contribute based on anticipated regulatory guidance? Symposium presented at the 35th International Conference on Pharmacoepidemiology and Therapeutic Risk Management. Philadelphia, PA, 27 August 2019.

or acceptability to patients of specified alternatives or choices among outcomes or other attributes that differ among alternative health interventions.”¹²

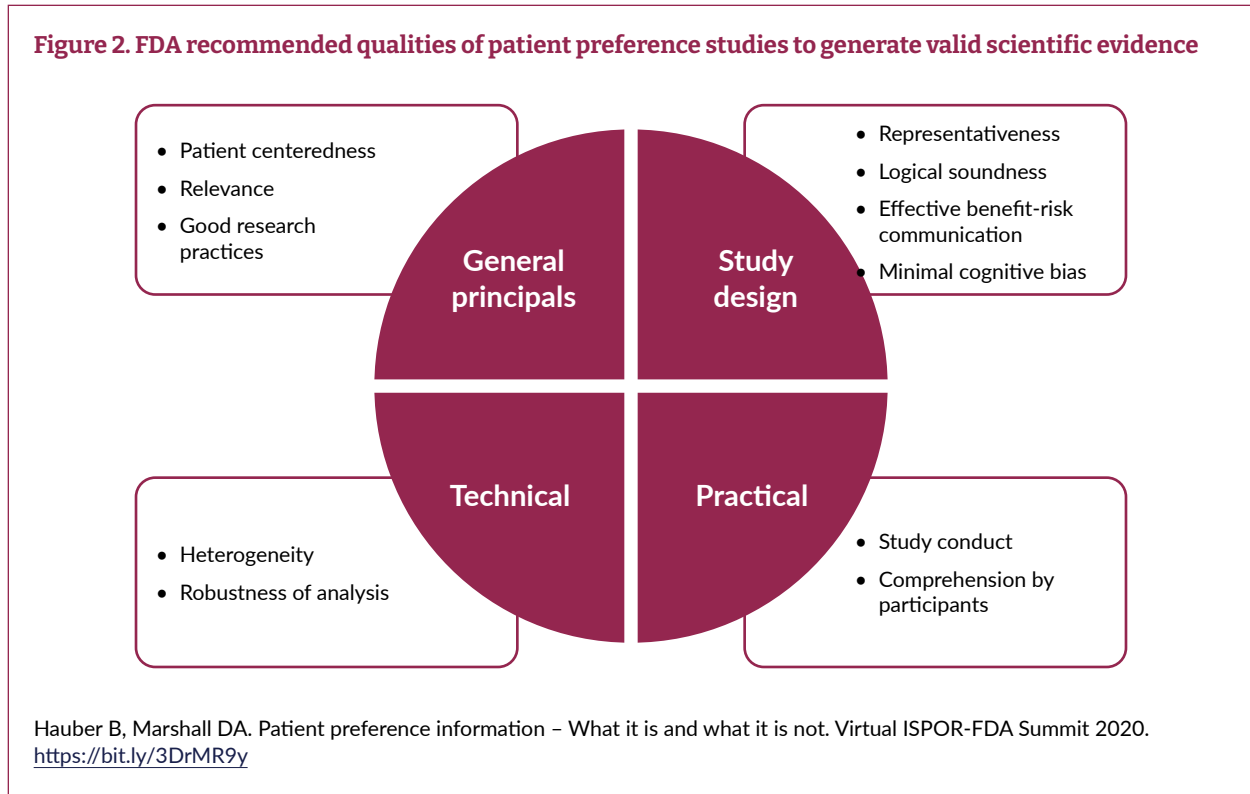
It is important to understand that PPI and PROs are different. PPI is an assessment of desirability or acceptability of an outcome or treatment alternative. It is a statement of what the patient wants and what a patient is willing to accept or to give up in order to get what is important to them. A PRO, by contrast, is a measure of a realized outcome and is a report of the patient’s health, or health status, which comes directly from the patient, without clinician or any other second party interpretation. It is a statement of “what is.”

It is also important to recognize that PPI is one subtype of patient experience data (PED).¹² PED can be data collected by anyone with the intention of providing information about the patient’s direct experience with a disease or condition. PED includes the experiences, perspectives, needs and priorities of a patient. This data may be about the symptoms of their condition or disease and its natural history; the impact of the condition on their functioning and qualitative of life; experience

with treatments and outcomes; and the relative importance of any issue defined by the patient as important.

Although health authorities such as FDA and EMA have expressed openness to using PPI to inform regulatory decisions, there is still work to be done before we realize the full potential of PPI. For example, sponsors and health authorities will benefit from the experience gained during the design, execution, analysis, and review of additional submissions that contain PPI. In addition, because PPI has its greatest utility in certain situations, generating PPI data is not always a good investment of time and other resources and it will therefore be important to understand in which types of situations PPI is likely to be most useful.

These learnings will help regulators provide guidance that increases certainty around expectations and increases consistency of advice to drug developers. The opportunity for early, timely, robust interactions between regulators and sponsors is critical for accelerating the successful use of PPI to inform regulatory decisions. Sponsors need to seek input from regulators as early as possible regarding proposed PPI studies and



proposed designs to ensure quality and relevance and to avoid unnecessary issues that later require changes. These changes can delay life-saving medicines from reaching patients and can further frustrate patients who shared their precious time to participate in the preference or other studies. Continued collaboration between regulators and sponsors will deliver important incremental advances in methods and best practices that can enhance utility of PPI in regulatory decision making.

Patient engagement at EMA

Two complementary elements are needed to ensure the patient voice is incorporated throughout drug development and associated evidence generation. They are patient engagement during regulatory assessments and patient experience data, developed as part of a marketing application submission.

Experience at EMA has shown that engaging with patients provides unique insights into everyday aspects

of living with a condition and helps understand disease and treatment burdens, unmet needs, preferences, and hopes for new therapies. These insights, combined with all other data, inform benefit-risk discussions and contribute to overall medicines assessment. Listening to patients’ experiences and preferences leads to more patient-relevant and meaningful outcomes, while increasing transparency, awareness and understanding of regulatory decisions.

Once more, generating and using patient experience data reinforces patient relevance in evidence generation by:

- Including patient preferences to inform benefit-risk assessment,
- Coordinating an approach to patient-reported outcomes and promoting core health-related, quality-of-life PROs;
- Updating existing and developing new guidelines on patient experience data collection and use at global level through multistakeholder collaboration;
- Encouraging use or incorporation of new digital tools to foster efficient data collection; and

- Working with health technology assessment bodies to optimize evidence generation can also address payers questions.

Including patient preferences could make drug development and regulation more relevant and cost effective, which could reduce the burden on health-care systems. EMA is actively working to advance the regulatory science and use of PPI through its participation in IMI PREFER.¹³ The goal of PREFER is to provide a set of systematic methodologies and recommendations to assess, engage, and include patient perspectives during the development, approval, and postapproval of new therapies. EMA released a draft qualification opinion¹⁴ of the IMI PREFER framework in late 2021 for public consultation. In addition, an International Council for Harmonisation (ICH) reflection paper on patient-focused drug development¹⁵ has proposed the development of new ICH guidelines for a harmonized approach to including patient per-

spective in a methodologically sound and sustainable way, thereby improving quality, relevance, safety, and efficiency of drug development to inform regulatory decision making.

The paper notes the focus should be on informing the drug development process using PROs and COAs to define clinically meaningful changes in outcomes. There should also be an emphasis on the trade-offs between benefits and harms and quantifying the importance of benefits and harms for patients by measuring those trade-offs. It is also important to acknowledge that such trade-offs may vary from patient to patient.

Today, individual patients' insights are commonly integrated within EMA assessments and the added value of their input has been demonstrated. Future goals include further strengthening patient engagement during regulatory assessments; enhancing the generation and use of patient experience data; providing guidance for multis-takeholder projects; and advancing patient engagement in a harmonized global context.

The FDA now considers use of patient input an important part of drug development that can foster innovation and enhance the availability of safe, effective drugs. Furthermore, patient input can help inform the therapeutic context for regulatory review; inform selection of clinical outcomes; ensure appropriateness of instruments used to collect trial data; and help ensure that investigations into the effects of treatments assess outcomes that are meaningful to patients.

**Patient voice in regulatory decision making:
An FDA perspective**

What has become clear through the FDA's experience in patient-focused drug development is that patients are "experts" in knowing what it is like to live with a serious, chronic condition because of their individual patient experiences. That unique and personal perspective can also be harnessed to inform to drug development and decisions made by clinicians, drug developers, regulators, and others.

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The role of patient experience data in regulatory decision making depends on several factors, including:

- The clinical context of the disease (i.e., the severity of condition and degree of unmet medical need);
- Whether the clinical outcome assessment, including the PRO tool that is used, is fit for purpose; and
- Whether patient preference studies provide patients with a balanced and unbiased presentation of the benefits and risks reported in the clinical trials, whether the cognitive burden of the judgment and trade-off tasks are reasonable, and other considerations.

Patients want therapies that work and they also want to be actively involved in advancing development of safe, effective therapies for their conditions and they want others to pay attention to their perspective and be respectful of their time.

The 2016 Cures Act¹⁶ defined patient experience data as that information collected by any persons, including patients, family members, caregivers of patients, patient advocacy organizations, disease research foundations, researchers, and drug manufacturers.

PED is intended to provide information about patients' experiences with a disease or condition, including the impact – both physical and psychosocial – of such disease or condition, as related to therapy or clinical investigation on patients' lives as well as patient preferences with respect to treatment of such disease or condition. In regulatory decision making, PED has the potential to help pose several questions, such as:

- How serious is this indicated condition, and why?
- How well is the patient population's medical need being met by currently available therapies?
- How meaningful is the therapeutic benefit, and for whom?
- How compelling is the expected benefit in the post-market setting?
- How serious are the “safety signals” identified in the submitted data?
- What potential risks could emerge in the post-market setting?

Whether PED can be used, and how it can be used, depends on the data's relevance, form, and quality. Quality data can provide powerful narratives and provide regulators with unique insights about clinical context and what matters to patients. Likewise, using methodologically sound measures and tools (COAs) to systematically capture what matters most during clinical trials can turn patient narratives into evidence for regulatory decision making. To facilitate the development and use of sound measures and approaches, the FDA is in the process of issuing a series of methodological PFDD guidance documents that cover:²

- Methods to collect patient experience data that are accurate and representative of the intended patient population;
- Approaches to identifying what is most important to patients with respect to their experience as it relates to burden of disease/condition and burden of treatment;
- Approaches to selecting, modifying, developing, and validating clinical outcome assessments (COAs) to measure outcomes of importance to patients in clinical trials; and
- Methods, standards, and technologies to collect and analyze COA data for regulatory decision making including selecting the COA-based endpoint and determining clinically meaningful change in that endpoint

Conclusion

There is an increasing recognition of patients' unique expertise and the importance of incorporating their perspectives into both drug development and clinical care. There is also an increasing awareness of the opportunities for PED to inform the clinical context of regulatory decision making. However, it is the relevance and quality of collected PED that will affect the extent to which it can be used in decision making. FDA, EMA, and other regulators (e.g., via ICH), are planning, developing, and publishing new guidances to help ensure that patient and sponsor efforts result in regulatory-grade data that is fit for the intended purpose and informs the regulatory decision. It is also a positive sign that regulators such as FDA and EMA are addressing

how PED will be used in benefit-risk assessment,¹⁷ and how this data will be communicated to health care providers, patients, and other stakeholders. Lastly, as the regulatory science of PFDD matures, it is important to focus on sustainability and global aspects. In terms of sustainability, the development of core sets of COAs^{9,10} that can be used for the same patient impact domains in multiple diseases have the potential to greatly reduce the resource burden that is currently associated with developing individual disease specific instruments. In addition, core set COAs that focus on functional elements may also be more easily shown to be appropriate for use globally. Global acceptance and harmonization of PED collection and analysis methodology will be an important step toward efficiently and consistently applying these PFDD principles to global drug development and will further increase the patient voice in informing regulatory decisions.

Acronyms and abbreviations

CDER, Center for Drug Evaluation and Research; **ClinRO**, clinician-reported outcome; **COA**, clinical outcome assessment; **EMA**, European Medicines Agency; **FDA**, [US] Food and Drug Administration; **HTA**, health technology assessment; **ICH**, International Council for Harmonisation; **ObsRO**, observer-reported outcome; **PED**, patient experience data; **PFDD**, patient-focused drug development; **PPI**, patient preference information; **PROs**, patient reported outcomes.

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Richard Jahn, JD, MS, leads Pfizer Inc's regulatory intelligence group, which provides asset teams with a competitive advantage by monitoring the external environment to identify opportunities and threats, and by delivering complex analyses that inform regulatory strategy. Jahn also drives regulatory policy development and advocacy for select topics, including patient-focused drug development. He has more than 20 years' experience in the pharmaceutical industry. Before joining Pfizer, he spent 16 years in various roles in regulatory strategy, policy, and intelligence at AstraZeneca, and has additional legal and scientific research experience. Jahn holds an LLM in health law, a JD focused on intellectual property, and master's degrees in biology and regulatory affairs. He can be reached at Richard.Jahn@pfizer.com

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Nathalie Bere, MPH, has been with the EMA since 1998 and is currently responsible for its engagement with patients and consumers. Patients bring specific knowledge and expertise to the scientific discussions from their real-life experience of living with a condition and their contributions lead to better regulatory outcomes. Over the years, she has been testing and implementing various methodologies to

include the patient's voice in all aspects of the regulatory lifecycle of a medicine. As a steady increase in patient engagement has been observed, EMA continues to further strengthen and diversify these activities and ensure they are fit for purpose in an evolving health landscape. Bere has a master's degree in public health and a bachelor of science degree in psychology. She can be reached at Nathalie.Bere@ema.europa.eu

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Acknowledgment This article was adapted from a presentation at RAPS Convergence 2021 on 14 September. Randolph Fillmore assisted in the preparation of the article. He can be reached at flasciencewriter@gmail.com

Citation Jahn R, et al. Patient-reported outcomes and patient preference information in regulatory decision making. *RF QUARTERLY*. 2021;1(4):4-13. Published online 13 December 2021. <https://raps.org/news-and-articles/news-articles/2021/12/patient-reported-outcomes-and-patient-preference-i>

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