European Federation of Pharmaceutical Industries and Associations

Draft ☐ Final ✱

EFPIA Position on Transparency of Patient Evidence in Regulatory Decision Making and Product Information

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Executive Summary

The Pharmaceutical Industry is increasingly including the views and perspectives of patients in all stages of drug development. The EMA has also recognised the importance of this by including patients representatives in its committees and decision-making processes. Both Industry and Regulators are now taking this a step further by leveraging scientific methodologies that enable a more structured and representative patient input so that patient preferences and outcomes that are meaningful to patients can be systematically considered and captured during product development. A significant indicator of this is the Reflection Paper on Patient-Focused Drug Development proposed by both EMA and FDA and endorsed by the ICH Assembly in November 2020.

Currently no clear guidance exists on how robust patient evidence can be generated and there is limited information available on how this evidence has been used during the regulatory assessment/for decision-making, and the impact it has had. To encourage and optimise implementation of a more evidence driven patient centric approach and provide useful information to patients, prescribers and other stakeholders, greater transparency is required.

EFPIA propose that transparency on how patient evidence has been considered in the regulatory decision as an explicit goal in the EMA plans for the development of patient centric drug development. Guidance should be provided on the criteria to ensure the patient evidence generated is adequately robust to be included in the regulatory decision-making process, in the regulatory review/decision documents (e.g. EPAR) and, where appropriate, in the product information.

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1. Introduction

A shared objective of key R&D stakeholders is to foster patient focused drug development and to allow the use of patient input in the form of evidence and preference to be reflected in Regulators' benefit risk assessments and HTA body appraisals.
An integral part of this is to ensure that patient evidence obtained during drug development and submitted to support the Marketing Authorisation Application (e.g., through Patient Preference studies, Qualitative methods or Clinical Outcome Assessments (COAs)[1]) is adequately and transparently reflected in the European Public Assessment Report (EPAR) and in the product SmPC (Summary of Product Characteristics), and ultimately in the package leaflet that is made available to patients. Such information is expected to:

- Encourage/incentivize patients' involvement in drug development and demonstrate its value;
- Provide drug developers with a better understanding of how patient evidence is used in regulatory decision making,
- Provide opportunity for developing and sharing best practice;
- Provide transparent insight/information to stakeholders e.g., healthcare providers (HCPs), Regulators, Health Technology Assessment (HTA) bodies, to enable downstream decision making;
- Provide information to patients and prescribers that could assist their shared decision-making and drive accountability to ensure patient perspective consideration in regulatory and shared physician-patient treatment decisions;
- Provide drug developers with a better understanding of how patient evidence is used in regulatory decision making;
- Provide opportunity for developing and sharing best practice.

2. Problem statement

While several major regulatory agencies have published (draft) guidance and reflections on the role of patient evidence in medicines development, there is currently no clear understanding of how/when patient evidence collected during drug development will be considered by Regulators to be sufficiently fit-for-purpose for benefit-risk decision making and/or inclusion in the regulatory documents and product information. Consequently, there is currently a lack of common approach of relevant patient evidence for a given condition.
It is equally important to understand when patient evidence was provided but **not** used in regulatory decision making. Such information would help inform sponsors and patient groups to collect and submit input likely to be most valuable and relevant to regulators. Although there are several completed and ongoing Innovative Medicines Initiative (IMI) projects and qualification

[1] See details in Annex 2 & 3.


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initiatives to clarify requirements (e.g., IMI PREFER), an overview of the types of patient evidence gathered and their reflection (or not) in the content of the product information across different regions is not available.

A report published by the FDA[2] on the "*Assessment of the Use of Patient Experience Data in Regulatory Decision-Making*" revealed that of the 176 approved new medicines (NDAs and BLAs) between June 2017 and June 2020, 30% mentioned patient experience data in the labelling, with COAs accounting for 92% of that data. However, applicants commented that the evidentiary standards for including patient evidence in labelling are unclear and that patient evidence does not often appear in labelling, except in some instances where specific PROs (Patient Reported Outcomes) or other COAs contributed to product approval. This limited transparency on when and how the patient perspective has impacted regulatory decision making, means the advantages and impacts outlined in the Introduction are not currently possible.

This paper outlines what has been done so far to advance the design and inclusion of patient focused evidence. It also summarises the key initiatives recognized as critical elements towards the development of robust methodologies for collecting Patient Evidence. These robust methodologies will provide high quality data which EMA can have confidence in during their decision making and consequently be confident to transparently reflect that data in the EPAR and Product Information. The paper then provides recommendations on how to systematically carry forward the patient's voice through regulatory decision making and into product labelling by further development and implementation of these initiatives.

3. Overview of some existing initiatives

To enable full transparency and inclusion of patient evidence in the EPAR and in the Product Information, regulators need to have greater confidence in the robustness and quality of this evidence. This increased confidence should result in its systematic and integral inclusion in benefit-risk decision making. There are specific developments which need to be delivered to address the problem outlined above. These developments are summarised in the diagram below and some of the most relevant initiatives which may enable or deliver these, are then described in detail in the following text.

[2] https://www.fda.gov/media/150405/download

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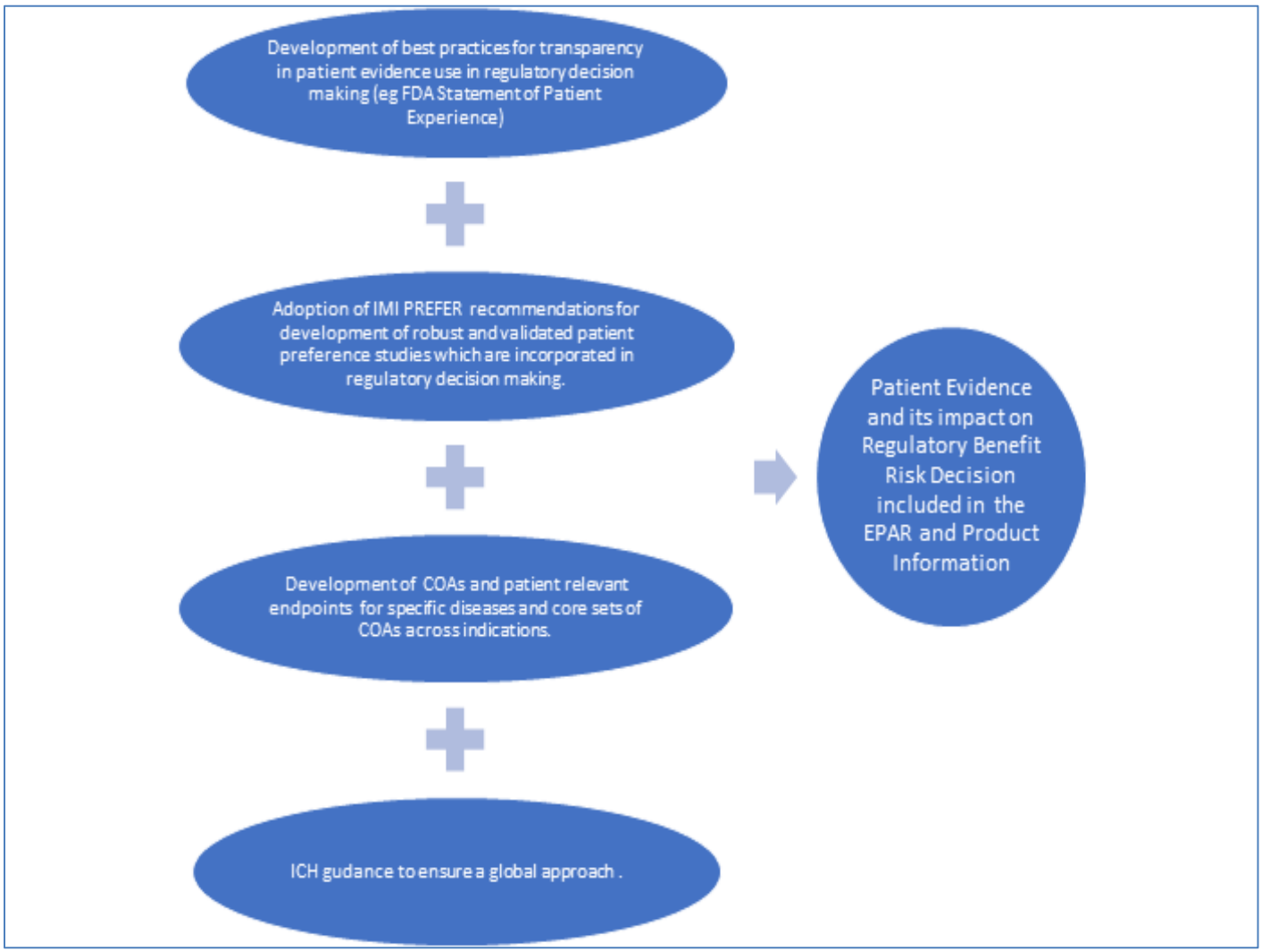

3.1 Systematic Research into Patient Preferences

Patient preference research has been investigated in the context of benefit risk and HTA decision making for quite some time. A recent public private partnership has provided significant progress in this area. IMI PREFER[3] which started in 2016 and published its recommendations in May 2022, is a 5-year public-private partnership research project developed under the IMI EU commission research agenda. The consortium objective was to strengthen patient-centric decision making by developing evidence-based recommendations to engage, include and assess patients' preferences during the development, approval, and post-approval of new medicines.

[3] https://www.imi-prefer.eu/

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The European Medicines Agency (EMA) and the EU network of HTA bodies (EunetHTA) jointly reviewed the framework for patient preference studies[4] proposed by the PREFER consortium within the EMA qualification framework (see Annex 2), followed by a publicly available EMA opinion[5]. The goal of the PREFER framework is to provide recommendations to support the development of guidelines concerning the inclusion of patient preferences in the Regulators benefit-risk assessment and HTA body appraisal of medicinal products and medical devices. In Oct 2021 EMA published the draft qualification opinion of IMI PREFER, and the final opinion[6] was published in May 2022.

Also, FDA and ICH have already outlined the relevance and potential value that patient evidence can have in medicine's development and regulatory decision making – including guidance to sponsors on how to ensure methods are sufficiently robust for regulatory purposes.

3.2 Overview of PRO development and methods to measure the patient experience such as COAs

Information on endpoints/outcomes which are important and most relevant to patients (as defined by patients themselves) in their daily life and not just traditional objective endpoints should also be considered

COAs are typically time and resource intensive to develop and qualify, and in some cases multiple COAs have been developed by different parties for the same or similar diseases or conditions. Traditionally COA instruments have been developed to be disease specific. If one considers the challenges of developing a specific COA for all diseases (i.e., a disease-agnostic COA), in particular when considering the number of different rare diseases, the challenge would be daunting. To advance this field, stakeholders need to focus on efficiency and feasibility: e.g., opportunities to develop COAs or PROs for symptoms across disorders, or more generally accepted instruments per disorder. This is where collaboration is of value and through public-private partnerships such as those established through the EU IMI.

The work achieved by the **IMI PROactive**[7] consortium is a good example of how to develop and qualify a PRO that can be used in the clinical practice and in clinical trials to ultimately support labelling claim.

[4]https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/chmp-eunethta-parallel-scientific-advice-qualification-framework-points-consider-method-selection_en.pdf
[5] https://www.ema.europa.eu/documents/regulatory-procedural-guideline/qualification-opinion-imi-prefer_en.pdf
[6] https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/qualification-opinion-imi-prefer_en.pdf
[7] https://www.imi.europa.eu/projects-results/project-factsheets/pro-active


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Physical activity (PA) has been recognized as one of the most common predictors of mortality in patients with chronic obstructive respiratory disease (COPD). Research has shown that patients who suffer from lung diseases reduce their PA levels, which has a noticeable impact in their social life. Since there were no validated tools to measure the impact of the disease on how patient experience PA, the PROactive consortium developed and qualified two innovative PROs , the C-PPAC and the D-PPAC, to capture both the experienced amount of PA and the difficulties during activities, opening the way for the development of effective therapies. Both tools, which were developed according to the state of the art as detailed in the 2009 FDA PRO guidance[8] to support labelling claim, are hybrid tools - combining information from questionnaire items and the readouts of an accelerometer.
While it took nearly seven years from the concept to the qualification, this was an opportunity for the consortium, which included not only public and private partners but also patient organisations and Small and Medium Enterprises (SMEs), to interact with the regulators. Two subsequent qualification advice procedures allowed the consortium to discuss with the regulators the progress made developing the tools and adapt their development to successfully qualify them for use as endpoints in clinical trials (EMA Qualification Opinion[9], April 2018).
Further to the qualification, the results of the ACTIVATE study which used the tool, were included in section 5.1 of the SmPC[10] of Duaklir Genuair (aclidinium/formoterol).

More recently, the goal of the **IMI MOBILISE-D[11] consortium**, is to identify and validate a specific set of Digital Mobility Outcomes (DMOs) to monitor and predict clinical outcomes in a variety of disease states, e.g., Parkinson's disease, COPD, multiple sclerosis, proximal femoral fracture, congestive heart failure; and to be used as reliable quantification of the mobility performance construct. So far, the project is on track as shown by the two Letters of Support[12,13] issued by EMA as a result of the qualification advice. The consortium is currently starting interactions with the FDA COA Division to enter the FDA Clinical Outcome Assessments (COA) Qualification Program.

EFPIA will explore opportunities such as those described above to further develop the concept through public-private partnerships since collaboration in the pre-competitive space has shown its value .

[8] https://www.fda.gov/media/77832/download
[9]https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/qualification-opinion-proactive-chronic-obstructive-pulmonary-disease-copd_en.pdf
[10] https://www.ema.europa.eu/en/documents/assessment-report/duaklir-genuair-epar-public-assessment-report_en.pdf
[11] https://www.mobilise-d.eu/
[12]https://www.ema.europa.eu/en/documents/other/letter-support-mobilise-d-digital-mobility-outcomes-monitoring-biomarkers_en.pdf
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3.3 Health Authorities activities

Reinforcing patient relevance in evidence generation is included in the EMA's Regulatory Science Strategy (RSS) to 2025[14]. See Annex 4 for more details.

In March 2021 the UK MHRA has also increased the emphasis on patient evidence in the assessment of applications for new active substances and new indications with a new pilot where marketing authorisation applicants are asked to provide evidence of any patient involvement activities during product development.

As part of its workplan to implement the 21st Century Cures Act the US FDA has reported[15] on the use of patient experience data in regulatory decision-making. FDA has conducted workshops and is developing a series of four methodological guidance documents. In addition, a further guideline on using relevant patient experience data and related information as part of benefit-risk assessment was released in September 2021 for 60-day public consultation[16]. The FDA approach and its guidance documents are detailed further in Annex 3. The recently published PDUFA VII Commitment letter also includes specific metrics and goals to further advance Patient-Focused Drug Development (PFDD) at the FDA.

The IMI PREFER project is referenced in the ICH Reflection Paper on Patient-Focused Drug development (PFDD) which was proposed by both EMA and FDA and endorsed by the ICH Assembly in November 2020[17]. This Reflection Paper identifies key areas where incorporation of the patient's perspective could improve the quality, relevance, safety and efficiency of drug development and inform regulatory decision making. It also presents opportunity for the development of new ICH guidelines to provide a globally harmonized approach to inclusion of the patient's perspective in a way that is methodologically sound and sustainable for both industry and regulatory authorities.

4. EFPIA position

The principle of transparency and the benefits of sharing information and experience in developing and using patient evidence, should be actively pursued by the EMA and all

[14]https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/ema-regulatory-science-2025-strategic-reflection_en.pdf
[15]https://www.fda.gov/drugs/development-approval-process-drugs/assessment-use-patient-experience-data-regulatory-decision-making
[16]https://www.fda.gov/regulatory-information/search-fda-guidance-documents/benefit-risk-assessment-new-drug-and-biological-products
[17]https://admin.ich.org/sites/default/files/2020-12/ICH_ReflectionPaper_PFDD_Endorsed-ForConsultation_2020_1118.pdf


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stakeholders working collaboratively. EFPIA proposes the following recommendations to the EMA:

1. Provide Transparency of Patient Evidence

While the EMA RSS to 2025 does refer to '*reinforcing patient relevance in evidence generation*', it does not include details or discussion on the topic of transparency and inclusion of patient evidence in either the EPAR or the Product Information (e.g., SmPC). Given the benefits highlighted above EFPIA proposes EMA to formally add this to their action plan for RSS to 2025 implementation as they develop the science further.

In the shorter term, inclusion of information in the EPAR could already include a summary of the patient input and evidence solicited by the EMA and its Committees during development and assessment, as well as any data already generated during drug development from patient preference studies or relevant COAs/PROs. A template for this could be developed as a first step and included the framework of the planned changes to the EU Assessment report structure outlined in the CHMP workplan for 2022. An insight in to how this patient evidence was used in the overall benefit-risk evaluation would be invaluable to industry and downstream stakeholders, rewarding to the patients who provided their time and resource while providing valuable information to prescribers and patients in their shared decision-making. The following elements should be included:

- A brief description of any Patient Evidence study objective, study design, and methods for collection of Patient Evidence Data that was submitted.
- Information on how CHMP considered the Patient Evidence and to what extent (including whether the Patient Evidence was included in the PI).
- If Patient Evidence was not considered in the context of a regulatory decision, provide rationale as to why this was not considered and what criteria were applied by reviewers to assess utility (e.g., Patient input/evidence was not representative of the targeted patient populations).

Not only existing opportunities for sharing information (such as through the EPAR/PI) should be developed/optimised, but also new, innovative opportunities or platforms should be considered (e.g., FDA Patient Voice initiative; (see section 3, Annex 3) and greater use of new platforms to share case studies e.g., IMI PARADIGM Reporting and Dissemination tool[18].

[18] https://imi-paradigm.eu/PEtoolbox/reporting-and-dissemination.pdf

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2. Develop Guidance on Patient Preference Studies with Specific Reference to Criteria for Inclusion in Product Information.

As new methodologies (such as Patient Preference Studies, see Annex 2) are developed in initiatives such as IMI PREFER, clear guidance should be provided so that this data can be considered in the decision-making and included in the Product Information (section 5.1 of the SmPC) to help prescribers, in discussion with patients, in their clinical practice.
The qualification opinion on IMI PREFER [19]does mention the inclusion of Patient Preference Studies (PPS) in regulatory documents and states that in principle, information on PPS may be included in the Clinical Overview or the EPAR or other relevant documents. However, inclusion of PPS in these documents would apply to cases where this information was either relevant to the regulatory decision and the benefit risk assessment, and/or where PPS data are relevant to inform prescribers and users of the medicinal product. In addition, it states that this decision would be on a case-by-case basis and would need to consider the validity and robustness of the data. Therefore, more guidance around Agency expectations for patient preference data is needed in order to bring transparency to the criteria for inclusion in the EPAR and labelling.

Guidance could also be developed on inclusion in the Patient Information Leaflet. This may be facilitated by the development of e-labelling where the length of the package leaflet is less of a barrier to including information on product benefits as well as risks.

3. Enable and Encourage Rapid Development of Methodological Sound COAs/PROs in Drug Development Suitable for Inclusion in the Product Information

In order to include this information in the PI for a larger range of diseases and products, it is key to achieve the sustained incorporation of COAs into drug development, and in particular of PRO, Observer-reported outcome (ObsRO) and Performance outcome (PerfO) measures (see Annex. 1). It is important not to assume a PRO is always superior to other types of COA in measuring an outcome relevant to patients.
This will then:

- Facilitate incorporating the patient perspective more sustainable.
- Enable development of publicly available standard core sets of measures of disease burden and treatment burden for a given area.
- Provide avenues to advance the use of patient input as an important part of drug development.

[19] https://www.ema.europa.eu/documents/regulatory-procedural-guideline/qualification-opinion-imi-prefer_en.pdf


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To achieve this, it will be necessary to build on the examples provided in section 3.2 above and, use the experience to reduce the overall timelines to develop PROs.

Development of innovative Drugs is a global endeavour and studies are globally conducted. As EMA and FDA develop guidance and processes in these key areas (Patient Preferences and COAs) it is critical to align them appropriately and consider best practices and learnings from other jurisdictions (including HTA bodies) and ensure global alignment through ICH . The ICH M4E provides the appropriate basis for transparent consideration of patient evidence in decisions on Benefit risk, further harmonisation efforts as announced by ICH when adapting the reflection paper are eagerly awaited.

5. ANNEX 1 – Definitions

In general, terms used in this paper are in line with the IMI PREFER Glossary[20].

Different jurisdictions and collaborative frameworks are applying a verity of terminologies. The terms used in this position paper are as follows:

- *Patient input is reflecting the need to consider the patient and caregiver perspective in medicines development and regulatory decision making*
- *Patient evidence reflect data that are scientifically and robustly collected with a view to form part of the total evidence package submitted to and assessed by regulatory agencies*
- *Patient evidence include patient preference studies, clinical outcomes assessments (incl PROs)*
- *In addition, patient evidence can consist of other patient experience data, such as defined by the FDA's PFDD guidance*

The term Patient Experience Data (PED) is defined as (FDA definition see Page 15): "*Data collected by any person (including patients, family members and care givers of patients, patient advocacy organizations, disease research foundations, researchers, and drug manufacturers) that are intended to provide information about patients experiences with a disease or condition. The term specifically includes data regarding a) the impact of the disease or condition, or a related therapy on patient's lives and b) patient preferences with respect to treatment of the disease and condition*."

[20] https://www.imi-prefer.eu/about/glossary/


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6. ANNEX 2 – COA definition and Background

A clinical outcome assessment is a measure that describes or reflects how a patient feels, functions, or survives. Types of COAs include:

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

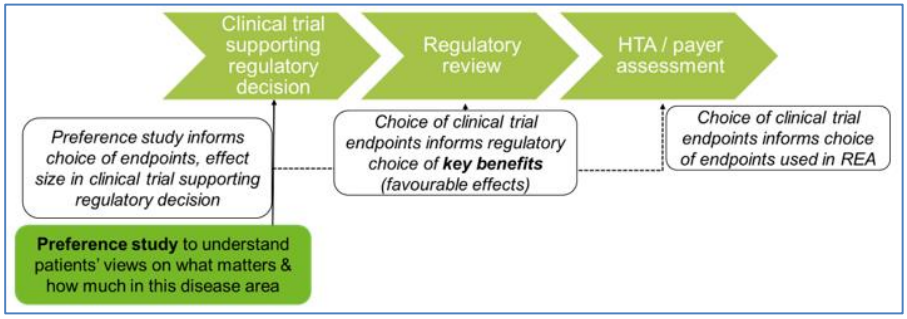
7. ANNEX 3 – IMI PREFER

IMI PREFER[21] which was initiated in 2016 is a 5-year public-private collaborative research project under the IMI.
The PREFER consortium involves 32 partners from academic institutions, patient organisations, HTA bodies, SMEs, patients' organisations and the pharmaceutical industry.

Patient preference studies can be used at critical decision points in drug development and product life cycle to find out:

1. What matters to patients?
2. How much does it matter?
3. What matters most? i.e. acceptability of trade-offs and uncertainty.

Example of how a patient preference study to inform the choice of endpoints can inform the clinical trial design, the regulatory assessment and the HTA/payer appraisal:



Example of how a patient preference study about acceptability of benefit-risk trade-offs can inform the regulatory assessment and the HTA/payer assessment:

[21] https://www.imi-prefer.eu/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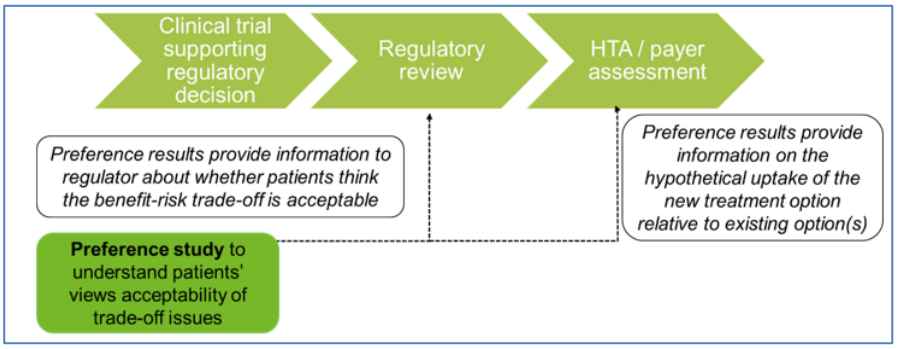

Choice of preference methods

Initially, a systematic literature search was used to identify available methods for exploring and eliciting patient preferences. Interviews and focus groups were then selected as the most promising and appropriate qualitative methods and in all PREFER case studies these explorative methods were used to initially investigate patient preferences before conducting quantitative studies (see Figure 1).

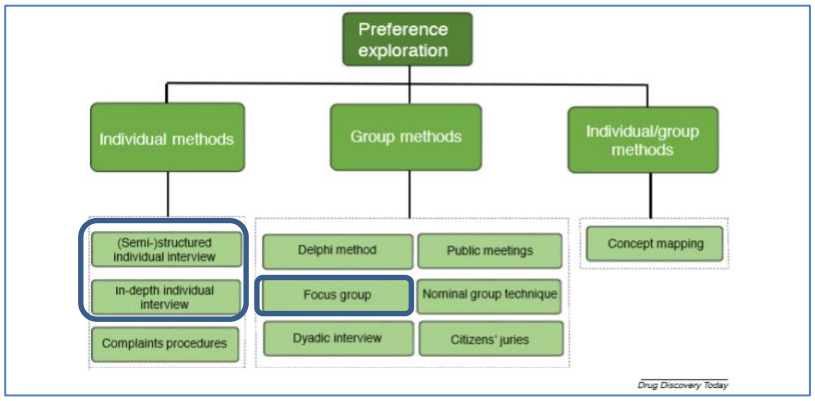

Figure 1. Methods to explore and elicit patient preferences in the product life cycle - Soekhai et al. 2019

To select the best quantitative methods for measuring patient preferences in the IMI PREFER case studies, a list of 35 criteria was developed to characterize and appraise the methods and Q-methodology was used to rank the criteria. An analytic hierarchy process (AHP) was applied to the highest-performing criteria to determine the relative importance of the criteria to each other so that finally 5 methods were identified as suitable for use in the PREFER case studies to answer the research questions (Figure 2).

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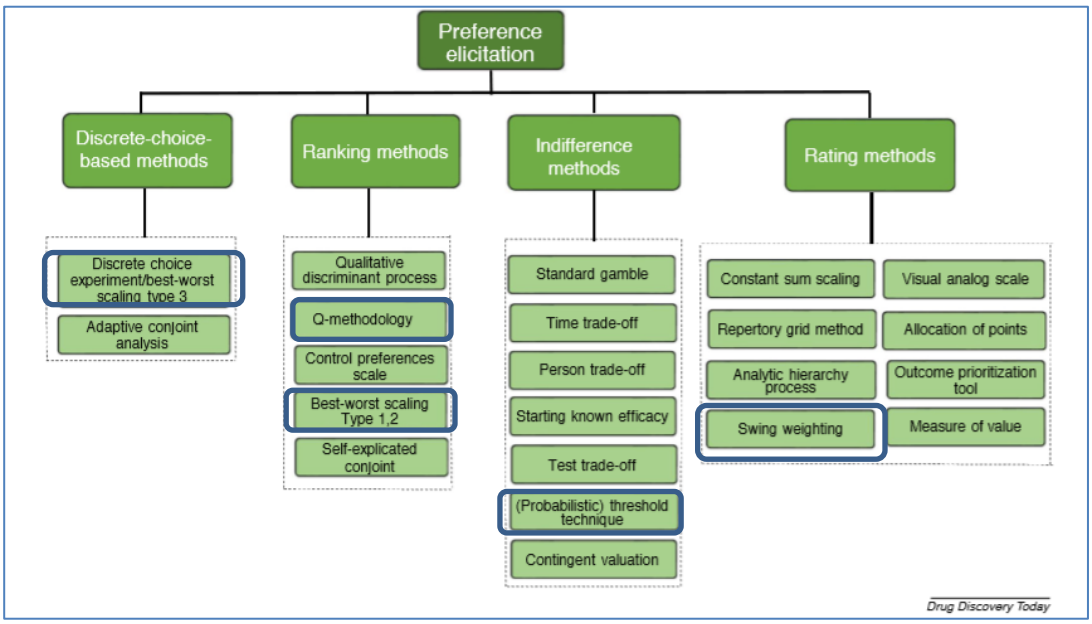

Figure 2. Methods to explore and elicit patient preferences in the product life cycle - Soekhai et al. 2019[22]

Decision on suitable case studies and method questions to investigate patient preferences was made according to criteria and methods questions detailed in Figure 3.

Criteria for case studies:

- Each PREFER case study addresses a ***preference-sensitive decision*** for one or more of the main stakeholders: Industry, HTA or Regulators
- Each case study involves DCE method and compares DCE to other methods (except 1 study in an ultrarare disease)
- Each case study consists of qualitative studies (interviews and focus groups) and a quantitative survey to assess benefit-risk tradeoffs and relative importance of different characteristics of a medicinal product or device

Prioritized method questions:

Method reliability:
- Comparison of methods

Impact of educational materials:
- Interactive, scenario-based features
- E-learnings on methods
- E-learnings on disease, attributes, levels

Generalizability of results:
- Heterogeneity
- Impact of psychosocial constructs

Figure 3. Criteria and method questions used to select the case studies

[22] https://doi.org/10.1016/j.drudis.2019.05.001


Eleven prospective patient preference studies have been included in IMI PREFER:

3 core academic case studies	5 additional academic case studies	3 industry case studies
•Rheumatoid Arthritis (RA) – PP for use of preventive medication in people at risk for developing RA •Neuromuscular Disorders (NMD) – Patient and caregiver unmet needs and risk tolerance for neuromuscular treatments •Lung cancer – PP on use of immunotherapy in lung cancer	•PP for glucose monitoring devices in diabetes •PP to assess value in gene therapies •Attribute attendance during completion of DCE in different disease populations •PP for biologics and JAK-inhibitors when changing RA treatment •PP in Multiple Myeloma including immunotherapies	•Relative importance of symptoms in COPD (Novartis) •PP for antithrombotic treatments following Myocardial Infarction (MSD) •PP for treatment of Osteo-Arthritis and lower back pain (Pfizer/ Lilly)

The results of the case studies were used to support the PREFER recommendations[23]. These consist of 8 sections that provide stakeholders with evidence-based insights into how patient preference studies should be designed, conducted, and used to inform decision-making throughout the medical product life cycle:

- Section 1 outlines the objective of the recommendations and introduces the different aspects and considerations for designing and conducting patient preference studies.
- Section 2 explains what information can be obtained from patient preference studies, and why and when these studies can be conducted and applied to medical product decision-making by industry, regulators, and HTA bodies and payers.
- Section 3 describes the PREFER framework for patient preference studies. The PREFER framework aims to inform study research teams on key considerations when designing, conducting, and applying the results of a fit-for-purpose preference study, and guide decision-makers when assessing and using preference study results to inform medical product decision-making.
- Section 4 focuses on the involvement of patients and other stakeholders, such as regulators and HTA bodies, in the design, conduct, and analysis of these studies so that the information they generate is meaningful for the patient population and useful for decision-makers.
- Section 5 focuses on different qualitative and quantitative preference methods and describes how stakeholders can select an appropriate method for a given context.
- Section 6 offers insights into when and how the psychological characteristics of participants, in addition to demographic and clinical variables, should be investigated so that preference heterogeneity among patients can be explored and understood.

[23] PREFER Recommendations - Why, when and how to assess and use patient preferences in medical product decision-making | Zenodo


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- Section 7 provides information on how to develop supporting materials so that patients can be educated about the questions and elements they are asked to evaluate and can make informed choices that will ensure validity and meaningfulness of the results.
- Section 8 provides insights into important avenues for further research, including recommendations for which topics and research questions should be explored and incentivised to further increase the quality of patient preference studies and gain wider consensus by all stakeholders involved

In addition, IMI PREFER received a qualification opinion[24] from the CHMP which agreed that the framework developed by IMI PRFER (section 3 of the recommendations) is suitable for informing on objectives, design, and conduct, and reporting of PPS. The case studies were also part of the EMA qualification procedure[25] for IMI PREFER, as these were used to explore a selection of available PPS methods (discrete choice experiment, best-worst scaling variants, swing weighting, threshold technique). The qualification opinion concluded that although the method selection is not exhaustive, the points to consider chapter of the qualification can support designing future PPS to generate evidence on patients' views with the goal of informing decision-making. However, the list of stated PPS methods shall not be considered prescriptive for PPS method selection.

The qualification opinion cannot pre-empt a case-by-case decision on the weight put on specific PPS results submitted as part of a marketing authorisation application. A decision on whether to include information on PPS in regulatory documents, such as the Clinical Overview, EPAR or other relevant documents would also be on a case-by-case basis and depend on whether the information was either relevant to the regulatory decision and the benefit-risk assessment, and/or where PPS data are relevant to inform prescribers and users of the medicinal product.

8. ANNEX 4 – EMA activities

An overview of EMA patient engagement activities is available on the EMA website[26].

Advancing patient-centred access to medicines in partnership with healthcare systems is one of the key goals of EMA's RSS to 2025 published earlier in 2020. Finding synergies with health technology assessment bodies on data generation during clinical development and post-authorisation studies is critical to fostering patient involvement and access to innovative medicines.

[24] https://www.ema.europa.eu/documents/regulatory-procedural-guideline/qualification-opinion-imi-prefer_en.pdf
[25] Draft Qualification Opinion of IMI PREFER - for public consultation (europa.eu)
[26] https://www.ema.europa.eu/en/partners-networks/patients-consumers

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In October 2020, for its 25th Anniversary, the EMA organised a virtual symposium to discuss new approaches to facilitating and using input from cancer patients to inform medicine development and regulatory decision-making. The purpose of the symposium was to identify opportunities and come up with recommendations to further advance patients' contribution and involvement in data collection, development and evaluation of cancer treatments, and help EMA to translate any recommendations into concrete actions to further improve cancer treatment development and regulation.

In January 2021, the EMA initiated a pilot phase[27] for early interactions with patients and consumer organisations. The EMA highlighted that this activity is in line with both the CHMP work plan objective to: '*Incorporate additional and regular processes to capture and include patients' views and preferences in the benefit/risk evaluations*', and EMA's RSS recommendations which highlight the need to enhance methods to systematically incorporate patient data in regulatory decision-making.

The framework for engagement[28] between EMA and patients and consumers (published in February 2022) and their organisations outlines the basis for involving patients and consumers in Agency's activities.

The framework aims at:

- supporting access to patients' real-life experiences of living with a condition, its management and the current use of medicines complementing the scientific evidence provided during the evaluation process.
- promoting the generation, collection and use of evidence-based patient experience data for benefit-risk decision-making.
- enhancing patients and consumers understanding of medicines regulation and their role in the process.
- contributing to efficient and targeted communication to patients and consumers to support their role in the safe and rational use of medicines and to foster trust in the EU Medicines Regulatory Network.

EMA also recently launched their Regulatory Science Research Needs initiative[29] which includes

- Developing standards for PROs to be used to assess the utilities of treatments in order to inform regulatory and potentially HTA decisions.

[27] https://www.ema.europa.eu/en/documents/other/pilot-phase-chmp-early-contact-patient/consumer-organisations_en.pd
[28]https://www.ema.europa.eu/en/documents/other/engagement-framework-european-medicines-agency-patients-consumers-their-organisations_en.pdf
[29] https://www.ema.europa.eu/en/news/ema-launches-regulatory-science-research-needs-initiative


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- Researching optimal approaches for patient input into the benefit-risk assessment in decision making.
- Researching and developing standards to incorporate patient preferences in the assessment of utilities of treatments to inform regulatory and potentially HTA decisions.
- Reviewing methodologies to be used to systematically gather and use patient data from the wider patient community during medicines' benefit-risk evaluation.
- Developing standards and quality requirements for designing, conducting, analysing, and reporting PRO studies for regulatory submission.
- Developing standards on quality requirements for designing, conducting, analysing, and reporting patient preference studies for regulatory submission.

9. ANNEX 5 – FDA activities

Section 3004 of the 21st Century Cures Act requires FDA to report on the use of patient experience data in regulatory decision-making. This legislation is also foundational because it defines what FDA means by "Patient Experience Data (PED)": Data collected by any person (including patients, family members and care givers of patients, patient advocacy organizations, disease research foundations, researchers, and drug manufacturers) that are intended to provide information about patients experiences with a disease or condition. The term specifically includes data regarding a) the impact of the disease or condition, or a related therapy on patient's lives and b) patient preferences with respect to treatment of the disease and condition.

The table below summarises the evolution of Patient Engagement at the FDA since 1988 and shows the FDA's commitment to dedicating resources to engage with patients.


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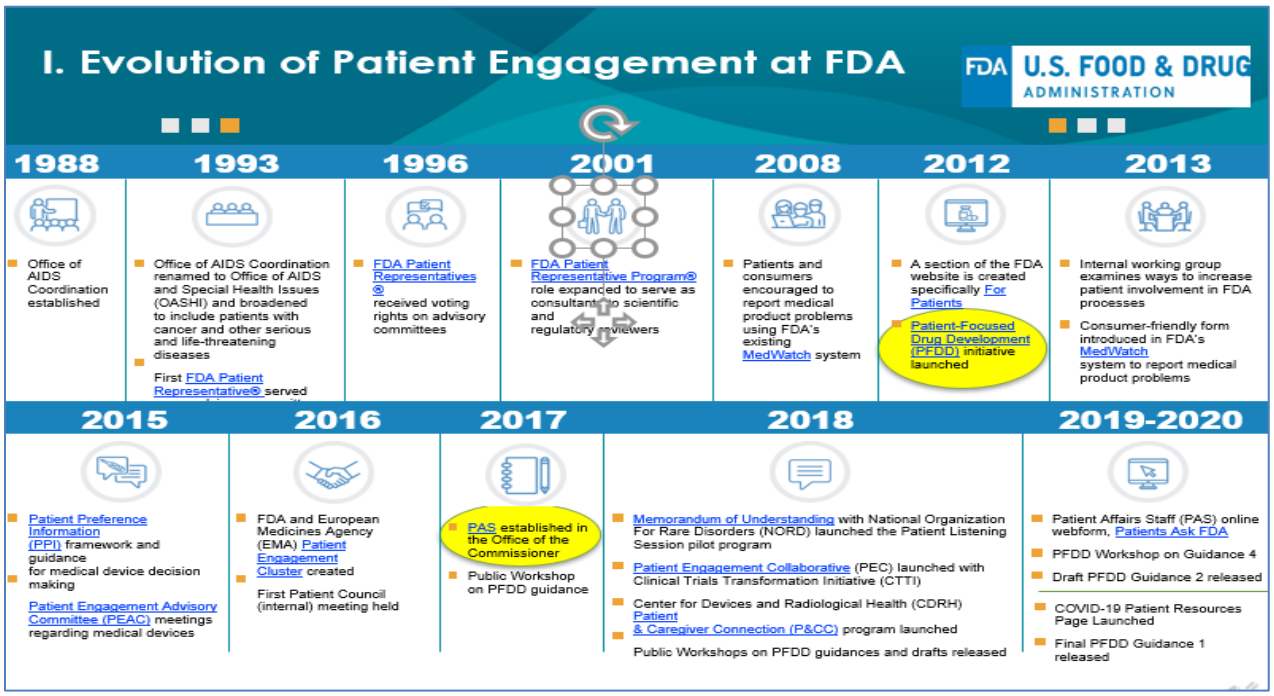

1. The FDA CDER Pilot Grant Program[30]

This program was established in 2019 to support the development of publicly available core set(s) of COAs and their related Endpoints for specific disease indications.
In 2019, the FDA made three awards under this grant program:

- the Migraine Clinical Outcome Assessment System (MiCOAS);
- the Clinical Outcome Assessments for Acute Pain Therapeutics in Infants and Young Children (COA APTIC); and
- the Northwestern University Clinical Outcome Assessment Team (NUCOAT) – this project will develop and validate COAs with applicability across a range of chronic conditions that assess physical function using patient-reported and performance outcomes.

More recently, on 29 April 2021, the FDA made two awards under this funding opportunity announcement. These awards will provide avenues to advance the use of patient input as an important part of drug development that can foster innovation and the availability of safe and effective drugs. One project expects to develop and establish a core set of COAs for nephrotic syndrome, with a primary focus on fluid overload; the second project is looking at measuring the communication ability of individuals with rare, neurodevelopmental disorders.

[30]https://www.fda.gov/drugs/development-approval-process-drugs/cder-pilot-grant-program-standard-core-clinical-outcome-assessments-coas-and-their-related-endpoints


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2. The FDA Statement of Patient Experience

In December 2016, the 21st Century Cures Act, (Section 3001) directed FDA to "*make public a brief statement regarding the patient experience data and related information, if any, submitted and reviewed as part of such applications*." FDA implemented the requirement by adding a table of patient experience data (PED) to Section 1.4 'Patient Experience Data of the FDA Multi-disciplinary Review and Evaluation' document, and this information is presented after the Benefit-Risk Assessment. This document continues to evolve as debate continues to evolve as more experience is gained with the aim of increasing its utility and value to stakeholders and to refine what information and detail is appropriate.

3. FDA Oncology Center of Excellence – Project Patient Voice Pilot

The Project Patient Voice[31], launched in June 2020 is a web-based platform for patients and caregivers along with their HCPs to communicate patient-reported symptom data to the FDA. The objective is to provide a consistent source of publicly available information describing patient reported symptoms collected from cancer trials for marketed treatments. The pilot is currently limited to one drug trial (Tagrisso registered in 2015). Whilst this data has historically been assessed by the FDA during the approval process, it is rarely included in the FDA prescribing information and is largely inaccessible to the public.
Making this data available can provide useful complementary information for HCPs, especially when talking about the risks and benefits of a drug. In this pilot, FDA will provide on their website information on patient-reported symptoms collected during the first six months of treatment in cancer clinical trials.

4. Patient Focused Drug Development Meetings

In 2012, the U.S. FDA established the Patient-Focused Drug Development (PFDD) initiative to obtain the patient perspective more systematically on specific diseases and their currently available treatments. Patient-Focused Drug Development (PFDD) meetings[32] are unique among FDA public meetings, with a format designed to engage patients and elicit their perspectives on two topic areas: (1) the most significant symptoms of their condition and the impact of the condition on daily life; and (2) their current approaches to treatment.

In addition to the formal PFDD public meetings, the FDA also hold Patient Listening Sessions[33]. Patient Listening Sessions can either be FDA-requested (where FDA has a specific set of questions to ask) or patient-led (when a patient community wants to share their perspectives with the

[31] https://www.fda.gov/about-fda/oncology-center-excellence/project-patient-voice
[32]https://www.fda.gov/industry/prescription-drug-user-fee-amendments/fda-led-patient-focused-drug-development-pfdd-public-eetings#:~:text=PFDD%20meetings%20are%20unique%20among,their%20current%20approaches%20to%20treatment.
[33] https://www.fda.gov/patients/learn-about-fda-patient-engagement/fda-patient-listening-session

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FDA). Patient Listening Sessions help the Agency inform product development, clinical trial design, patient preferences, and shape regulatory thinking. During a Patient Listening Session, FDA staff will either ask questions or simply listen to better understand patients' experiences and perspectives. Only the FDA, patients, caregivers, advocates, and community representatives participate in the session.

5. FDA Guidance documents

FDA is planning to publish a series of guidance documents intended to facilitate the advancement and use of systematic approaches to collect and use robust and meaningful patient and caregiver input that can better inform medical product development and regulatory decision-making. Two guidance documents have been published so far, and two others are expected shortly.
The topics and questions addressed by each guidance document are detailed below.

➢ ***Guidance 1:*** **2020 Guidance [34] on Collecting Comprehensive and Representative Input**
From whom do you get input, and why? How do you collect the information? This guidance discusses sampling methods that could be used when planning a study to collect patient input. It also provides a general overview of the relationship between potential research question(s) and method(s) when deciding from whom to get input (including defining the target population and development of the sampling strategy). The FDA held a public workshop[35] in Dec. 2020 to obtain feedback from stakeholders on considerations for:

1. Standardised nomenclature and terminologies for patient-focused drug development[36];
2. Methods to collect meaningful patient input throughout the drug development process.
3. Methodological consideration for data collection, reporting, management, and analysis of patient input.

➢ ***Guidance 2:*** **2019 Final Guidance[37] on Methods to identify what is important to patients**
This guidance discusses methods for eliciting information from individuals identified in Guidance 1, gathering information about what aspects of symptoms, impacts of their disease, and other issues are important to patients. It discusses best practices in how to do qualitative research including conducting interviews, development of interview guides, selection of types of survey questions, and considerations for collecting demographics and survey information. It also discusses survey methods and qualitative research topics to help avoid misleading results such as inadvertently priming patients in ways that can lead to results that poorly represent what is important to patients.

[34] https://www.fda.gov/media/139088/download
[35]https://www.fda.gov/drugs/news-events-human-drugs/public-workshop-patient-focused-drug-development-guidance-1-collecting-comprehensive-and
[36]Glossary:https://www.fda.gov/drugs/development-approval-process-drugs/patient-focused-drug-development-glossary
[37] https://www.fda.gov/media/131230/download


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➢ ***Guidance 3:*** **Selecting, Developing or Modifying Fit-for-Purpose Clinical Outcomes Assessments**

This guidance will address refining the list of important impacts and concepts from patients to develop potential study instruments. Given that not everything identified as important by patients, caregivers, and clinicians can demonstrate change in a specific treatment trial or is measurable, how will you select what to measure in a medical product development program to show clinical benefit? How will you identify or develop fit-for-purpose COAs to assess outcomes of importance to patients?

A public workshop[38] was held in 2018 to discuss Guidance 2 and Guidance 3 topics.

➢ ***Guidance 4:*** **Incorporating CoA into Endpoints for Regulatory Decision-Making**

This guidance will address methodologies, standards, and technologies that may be used for the collection, capture, storage, and analysis of COA data. The guidance will also address methods to better incorporate COAs into endpoints that are considered significantly robust for regulatory decision-making. This includes methods to define meaningful change in a COA-based endpoint and interpretation of results. The guidance will include information on the format and content required for regulatory submissions incorporating

patient experience, COA data. Guidance 4 topics were discussed in a public workshop[39] in Dec. 2019.

Specific to oncology development, the FDA issued in June 2021, a draft guidance on Core Patients-Reported Outcomes in Cancer Clinical Trials. This guidance is intended to improve the quality and consistency of data to inform patients with cancer about the symptoms and impacts they may experience during treatment with a cancer therapy. This as a result of a sustained effort to identify methods to rigorously collect PROs in cancer clinical trials. FDA has indeed been engaging with patients and outcomes research experts through a series of public workshops and publications on which outcomes to measure, how frequently to assess them and the tools available to do so.

6. PDUFA VII Commitments

The PDUFA VII commitment letter continues this embrace of PFDD and patient engagement by including several specific performance goals[40] within the package.

The commitment letter recognizes the growing interest in applying PFDD to development of cell and gene-based therapies, which are overseen by the Center for Biologics Evaluation and

[38]https://www.fda.gov/drugs/news-events-human-drugs/patient-focused-drug-development-guidance-methods-identify-what-important-patients-and-select

[39]https://www.fda.gov/drugs/development-approval-process-drugs/public-workshop-patient-focused-drug-development-guidance-4-incorporating-clinical-outcome

[40] https://www.fda.gov/media/151712/download


Research (CBER), in addition to its extant incorporation for small molecules and biologics. Much of FDA's patient engagement agenda has to-date resided within the Center for Drug Research and Evaluation (CDER) and the Center for Devices and Radiological Health (CDRH).

To expand PFDD into gene and cell-based therapy reviews, the performance letter commits CBER to convening a PFDD meeting by the end of FY 2023 "to better understand patient perspectives on gene therapy products, including cell-mediated gene therapy." The meeting will include a report and will explore whether tools or methods are needed to capture patient experience data pertaining to such therapies.

Beyond this performance metric, the commitment letter includes several other criteria that FDA says, "*will build on the successes of its efforts on Patient Focused Drug Development (PFDD), benefit-risk assessment in regulatory decision making, and the drug development tools qualification pathway for biomarkers*." Specific metrics contained in the letter include:

- Consulting with external experts by using the Intergovernmental Personnel Act to support review of patient experience data.
- Expanding outreach to internal personnel and sponsors, including with guidance, to build understanding and use of such approaches in regulatory reviews.
- Issue a Request for Information (RFI) by June 2023 on "methodological issues, including the submission and evaluation of patient experience data in the context of the benefit-risk assessment and product labelling."
- Convene at least two workshops focused on methodological issues during FY 24 and FY 25 and summarize priorities emanating from the RFI and workshops by the end of FY 26.
- By the end of FY 26, publish a draft guidance "on use and submission of patient preference information to support regulatory decision making" with a goal of issuing final guidance within 16 months from the close of the comment period.

In addition to these concrete metrics, the commitment letter speaks to work FDA has done to incorporate benefit-risk assessments, which incorporate patient preference data as part of the review process, including the work by CDER to include the benefit-risk framework within review templates. FDA did not make specific commitments pertaining to advancing the benefit-risk assessment through legislation currently before Congress, known as the BENEFIT Act, that would incorporate in statute PFDD and related data as a component of these assessments, as well as obligate tracking and transparency of such measures

7. Other FDA Initiatives

The Patient Engagement Collaborative (PEC) is a group of patient organizations and individual representatives who discuss how to achieve more meaningful patient engagement in medical product development and other regulatory discussions at the FDA.


The PEC[41] was established by the FDA and the Clinical Trials Transformation Initiative (CTTI[42]), a public-private partnership that brings together organizations and individuals representing academia, clinical investigators, government and regulatory agencies, industry, institutional review boards, patient advocacy groups and others to develop evidence-based solutions to clinical research challenges.

CDRH Patient Preference Initiative focused on developing the science of patient preferences for medical devices[43].

[41] https://www.fda.gov/patients/learn-about-fda-patient-engagement/patient-engagement-collaborative

[42] https://ctti-clinicaltrials.org/

[43]https://www.fda.gov/about-fda/cdrh-patient-science-and-engagement-program/patient-preference-information-ppi-medical-device-decision-making

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