Universidade de Lisboa
Faculdade de Farmácia

Methodologies on collection and use of patient experience data for medicines' regulatory assessment

Ana Pedro António

Monografia orientada pela Professora Doutora Carla de Matos Torre,
Categoria Professora Auxiliar Convidada.

Mestrado Integrado em Ciências Farmacêuticas

2022

Universidade de Lisboa

Faculdade de Farmácia

Methodologies on collection and use of patient experience data for medicines' regulatory assessment

Ana Pedro António

Trabalho Final de Mestrado Integrado em Ciências Farmacêuticas apresentado à Universidade de Lisboa através da Faculdade de Farmácia

Monografia orientada pela Professora Doutora Carla de Matos Torre,
Categoria Professora Auxiliar Convidada.

2022

Resumo

A perspetiva dos doentes é considerada cada vez mais importante nas tomadas de decisão ao longo do ciclo de vida do medicamento. Deste modo, tem-se vindo a investigar as melhores abordagens para recolher dados da experiência de doentes para informar processos de tomada de decisão que sejam centrados nos mesmos.

O presente estudo tem como objetivo apresentar uma visão geral de duas metodologias usadas na recolha de dados da experiência dos doentes: resultados reportados pelos doentes e preferências dos doentes (das expressões originais na língua inglesa "patient-reported outcomes" e "patient preferences", respetivamente). No contexto deste objetivo, este estudo propõe-se ainda a apresentar um estudo de caso sobre o uso destas metodologias no mieloma múltiplo com o intuito de discutir exemplos reais da sua contribuição para melhor informar os processos de tomada de decisão.

Uma pesquisa bibliográfica foi realizada na base de dados *PubMed* em dezembro de 2021 e posteriormente em agosto de 2022 para identificar artigos que abordassem o uso de dados da experiência dos doentes, resultados reportados pelos doentes e preferências dos doentes ao longo do ciclo de vida do medicamento. Adicionalmente, foi realizada uma pesquisa no motor de busca *Google* entre janeiro e agosto de 2022 para identificar literatura cinzenta relevante. Posteriormente, os documentos identificados foram selecionados com base nos critérios de seleção. Finalmente, a bibliografia dos artigos selecionados foi revista para identificar publicações adicionais.

Tomando como ponto de partida uma breve apresentação sobre dados da experiência dos doentes, este trabalho discute a utilização de dados reportados pelos doentes e de preferências dos doentes, descrevendo os seus potenciais papéis ao longo do ciclo de vida do medicamento, principais aspetos metodológicos, desafios, iniciativas recentes e recomendações, conforme descrito na literatura.

As referidas metodologias têm o potencial de informar várias etapas do ciclo de vida do medicamento. No entanto, existem ainda alguns desafios por ultrapassar. É impreterível fomentar a colaboração internacional e desenvolver orientações claras e harmonizadas. Só assim será possível incluir eficaz e sistematicamente a voz dos doentes no desenvolvimento de medicamentos e na prestação de cuidados de saúde que verdadeiramente valorizem as suas necessidades, prioridades e valores.

Palavras-chave: Dados da experiência de doentes; Resultados reportados pelos doentes; Preferências dos doentes; Ciclo de vida do medicamento; Mieloma múltiplo.

Abstract

Patients' perspective has become increasingly important in decision-making throughout the medical product life cycle. Therefore, multiple stakeholders are investigating the best approaches to collect patient experience data to inform patient-centric decision-making processes.

The objective of the present study is to provide an overview of the landscape regarding two methodologies used for the collection of patient experience data: patient-reported outcomes and patient preferences. Drawing on the knowledge from this overview, an additional objective of this study is to present a case study on the use of patient-reported outcomes and patient preferences in multiple myeloma to discuss real examples of the contribution of these methods for better informing decision-making.

A literature search was conducted on PubMed in December 2021 and August 2022 to identify articles addressing the use of patient experience data, patient-reported outcomes, and patient preferences in the context of decision-making throughout the medical product life cycle. Moreover, a Google search was conducted between January 2022 and August 2022 to identify grey literature relevant to the research objectives. Identified documents were screened in a two-step approach based on the selection criteria. Finally, references in selected articles were hand-searched to identify additional publications.

Taking as a starting point a brief discussion of patient experience data, this work discusses PROs and patient preferences input over recent years by describing their potential roles throughout the medicines' life cycle, main methodological aspects, challenges, ongoing efforts and initiatives to advance research and implementation, and key recommendations for future research, as reported by the literature.

The increased focus on patient engagement has been proved by the growing literature and initiatives on this subject. In fact, patient-reported outcomes and patient preferences have the potential to inform multiple key steps of the medical product life cycle. However, these methodologies face some challenges that have yet to be addressed. It is vitally important to foster international multistakeholder collaboration and develop clear and harmonized guidance for the use of patient-reported outcomes and patient preferences. Once this is achieved, it is expected that systematic and effective collection, analyses, and sharing of patient input will maximise its utility and greatly improve patients' lives.

Keywords: Patient experience data; Patient-Reported Outcomes; Patient Preferences; Medical product life cycle; Multiple myeloma.

Acknowledgements

Firstly, I would like to address a special thank you to Professor Carla Torre, who guided me throughout this project. I am extremely grateful for her support, guidance, and encouragement and for being ever caring, and attentive. I feel incredibly lucky for our paths to have crossed, and for having learned so much from her since then. Her unconditional generosity and dedication to her students will always inspire me.

Furthermore, I wish to express my deepest gratitude to my family. It was because of their unwavering support and love that today I can celebrate and dedicate this thesis to them. Words cannot do justice to the overflowing gratitude I feel.

Finally, a thank you to my dear friends, for being my companions on this journey, through thick and thin, and always with a good laugh.

Abbreviatures

BWS – Best-Worst Scaling

COA – Clinical Outcomes Assessment

CONSORT-PRO - Consolidated Standards of Reporting Trials Statement-PRO extension

DCE – Discrete Choice Experiment

DDT – Drug Development Tool

FDA – Food and Drug Administration

EMA – European Medicines Agency

EHR – Electronic Health Records

ePRO – Electronic Patient-Reported Outcome

EUnetHTA - European network for Health Technology Assessment

EUPATI - European Patients' Academy

FACILITATE – Framework for Clinical Trial Participants' Data Reutilisation for a Fully Transparent and Ethical Ecosystem

HTA – Health Technology Assessment

HRQL – Health-Related Quality of Life

HRQoL – Health-Related Quality of Life

HTAi - Health Technology Assessment International

IMI – Innovative Medicines Initiative

IQWiG – German Institute for Quality and Effi- ciency in Health Care

ISOQOL - International Society for Quality of Life Research

ISPOR - International Society for Pharmacoeconomics and Outcomes Research

MACBETH – Measuring Attractiveness by a Categorical Based Evaluation Technique

MDIC – Medical Device Innovation Consortium

MM – Multiple Myeloma

MPLC – Medical Product Life Cycle

NICE – National Institute for Health and Care Excellence

PARADIGM – Patients Active in Research and Dialogues for an Improved Generation of Medicines

PCORI – Patient-Centered Outcomes Research Institute

PEM Suite - Patient Engagement Management Suite

PFDD – Patient-Focused Drug Development

PFMD – Patient Focused Medicines Development

PGHD – Patient-Generated Health Data

PREFER – Patient Preferences in Benefit–Risk Assessments during the Drug Life Cycle project

PRO – Patient-Reported Outcome

PROM – Patient-Reported Outcomes Measure

PROTEUS – Patient-Reported Outcomes Tools: Engaging Users & Stakeholders

RCT – Randomized Clinical Trial

R&D – Research and Development

SISAQOL - Setting International Standards in Analysing Patient-Reported Outcomes and Quality of Life Endpoints Data

SmPCs – Summaries of Product Characteristics

SPIRIT-PRO – Standard Protocol Items: Recommendations for Interventional Trials in Patient-Reported Outcomes

Index

Figure Index

Table Index

Appendix Index

1 Introduction: Overview of Patient Experience Data

The increased focus on patient experience/engagement emerges from the goal to improve patient-centric decision-making throughout the medical product life cycle (MPLC) (1). This paradigm shift from disease-centred to patient-centred originates from the notion that patients are the experts in their own experience regarding their disease/condition and treatments. Moreover, since patients are the ultimate users of medical products, they should participate in the decisions that directly affect their care by incorporating patient experience into regulatory and clinical care decisions (2).

Patient engagement is defined by the Food and Drug Administration (FDA) as "*activities that involve patient stakeholders sharing their experiences, perspectives, needs, and priorities that help inform*" regulators, Health Technology Assessment (HTA) bodies, among others. This so-called patient experience data includes information concerning symptoms and natural history of the disease, the impact/experience of a given disease and its treatment on patients' functioning and quality of life, patient preferences for outcomes and treatments, and their point of view regarding unmet medical needs (Figure 1) (3–5).

A related concept to patient data is patient-generated health data (PGHD), defined as health data collected by patients themselves (or when appropriate, by their caregivers), including health history, disease symptoms, treatment history, biometric data, lifestyle choices, and patient-reported measures (PROMs). Examples of Patient-Generated Health Data (PGHD) include data collected through smartphone applications or other devices (*e.g.*, blood glucose monitoring using home health devices/biosensors, exercise and diet tracking using fitness monitors or mobile applications), and self-reported questionnaires about treatment side effects. PGHD has the advantage of being able to be collected outside the clinical setting, providing longitudinal data (with multiple time points of assessment) in-between medical visits in the real-world context.

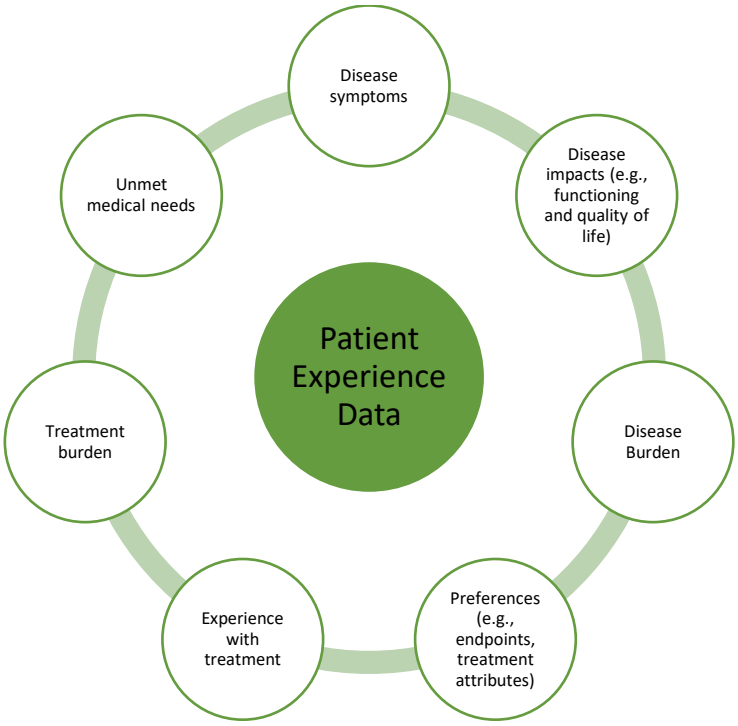

Figure 1. Examples of patient experience data. Adapted from FDA (2).

Several authors advocate the need for patients to be at the heart of the medicine's development and evaluation processes, and that they should be engaged early in medicine development, as their perspectives and experiences can help guide the decision-making process (*e.g.*, clinical trial design, selection of endpoints, and benefit-risk assessment) (6–9). However, currently, the patient perspective is not yet entirely part of the formal assessment (6).

Despite the added value recognized, patient engagement faces some challenges that have yet to be addressed. Some of the current challenges related to patient engagement implementation are summarized in table 1.

Table 1. Challenges of patient engagement. Adapted from Hoos *et al.* and Lowe *et al.* (10,11).

Timing and budget concerns	Unknown return on investment from patient engagement activities
	Institutional review board approval
	The rapidity of medicine development

	Development and validation of patient engagement tools (*e.g.*, PROs) is often slow and expensive
Compliance and regulatory challenges	Unavailable/few guidance for industry and regulators
	Regulators slow or reluctant to adopt patient-generated data and real-world data
	No regulatory requirement to involve patients in medicine development
	Legal and regulatory restrictions on the industry's communication with patients
	Lack of uniform, systematic, and robust methods for patient involvement
Methodological challenges	Risk for clinical trials to become unblinded
	Patient views may conflict with regulators, clinicians, and researchers
Organizational and clinical inertia	Inconsistent practices within and across stakeholders
	Resistance to change from clinicians and researchers
	Uncertainty regarding the feasibility of involving patients
	Uncertainty regarding the most suitable methods for involving patients
Negative perceptions	Concerns regarding patient capability to participate in complex medicine development conversations
	Tokenism in patient engagement (*e.g.* patients may be involved but their input is not truly taken into account)
	Perception of patient engagement as a soft science
	Need for a culture change to acknowledge the importance of patient engagement
Evidence	Lack of robust evidence of the benefits and value of patient engagement

Patient experience data has yet to be globally collected with systematic, robust, and consensual methods and there are uncertainties of how this information may be of best value to regulatory decision-making. As highlighted by Simon *et al.*, the challenge lies in developing methods that accurately capture and quantify the patient experience and preferences with minimal burden (6).

Notwithstanding the lack of a global framework, different stakeholders are engaging in efforts towards this goal. Appendix 1 provides a brief description of examples of recent patient engagement initiatives. On the other hand, regulators are also joining efforts for enhancing meaningful engagement, which will be discussed in subsequent chapters.

Still, rather than individual stakeholder initiatives, a multistakeholder effort is necessary to truly advance patient engagement. One example of such collaborative efforts is the FDA/EMA Patient Engagement Cluster, a workgroup established in 2016 to exchange best practices on patient engagement along the medical product life cycle. The idea underpinning the creation of this cluster workgroup is that a strengthen international collaboration will further enhance the Agencies' engagement activities with patients. This is operationalized through regularly scheduled teleconferences (expectedly 4 times *per* year) (12,13).

The evolving dialogue between patients and other stakeholders is expected to promote a culture of partnership which can improve decision making regarding efficacy, safety and cost-effectiveness analysis, prioritize the most valuable outcomes for patients, increase decision transparency, and guarantee patient satisfaction by aligning the development of novel medicines with patients' needs (14).

Integrating the patient voice in medicines development and evaluation requires appropriate methods for collecting patients' experiences and perspectives. It has not been yet defined a globally accepted set of methods for this purpose. Notwithstanding, the second guidance issued by FDA in a series of four methodological patient-focused drug development (PFDD) guidance documents discusses methods for collecting and using patient experience data and best practices. This guidance focuses on qualitative, quantitative, and mixed methods. A brief description of each method and respective examples are presented in table 2. The selection of the most suitable method should be guided by the research objective(s) and question(s), target population characteristics, and strengths and limitations of each approach (15).

Table 2. Methods for collecting patients' experience (15,16).

	Qualitative Methods	**Quantitative Methods**	**Mixed Methods**
Method description	Uses direct communication to obtain a deeper understanding of the patient's experience. Provides unstructured in-depth data about the patient's experiences, priorities, preferences, feelings and needs, capturing the exact words of the reporter.	Collects quantifiable data (*e.g.*, numerical data) which is interpreted and analysed through the application of statistical methods. Thus, quantitative approaches enable measurement, comparation, or description of patient experience information.	Combines the use of qualitative and quantitative methods. Qualitative and quantitative methods can be used concurrently or sequentially, provided they are analysed and interpreted together. This approach may be selected to confirm results from different methods, to investigate existing inconsistencies, or when different methods yield complementary data.
Examples	One-on-one interviews (semi-structured, structured and unstructured); focus groups; Delphi panels; facilitated discussions in organized patient conferences/meetings; observations of patient behaviour or events	Survey or questionnaire	Survey instruments with open-ended and fixed-response questions; interviews combined with administration of a survey instrument with fixed-response questions.

	(*e.g.*, social media listening).		
Administration methods	In-person; telephone; online/virtual video conferences.	Self-administered: paper-based, telephone-based, or electronic-based; Interviewer-administered: in-person or remotely.	

Aside from the methods previously mentioned for data collection, data can also be collected via passive or active means. Passive data, as the name implies, is collected without active participation or interaction from the patient. Examples of passive data include sensors in wearable and mobile devices or social media. On the other hand, active data collection requires the patient willingness to actively provide data (*e.g.*, data entry, or survey completion) (15,17).

Technology provides a unique opportunity for boosting passive and active patient data collection. For instance, PGHD provided by personal devices (*e.g.*, smartphones and smartwatches) can passively collect relevant data to inform a trial. These devices can hold even greater potential when paired with medical devices or active collection methods in order to fully understand patients' experiences with a disease and/or treatment. This enables a continuous flow of data generated with less burden for patients, that otherwise would not be possible in a conventional in-clinical assessment context. However, operational, and ethical constraints, such as collection of sensitive data (*e.g.*, location), and missing data, are preventing the acceptance of such data for regulatory purposes, which means that meaningful/relevant data on patient experience is continuously being wasted (15).

As previously mentioned, patient experience data needs to be captured through suitable and robust methods to be proved useful. Two distinctive but complementary types of patient experience data are growing interest among multiple stakeholders, named patient-reported outcomes and patient preferences, which will be further discussed in the following chapters.

2 Objectives

The aim of the present thesis was to provide an overview of the landscape regarding the patient experience data use in decision-making throughout the MPLC, with a focus on the following collection methods: patient-reported outcomes (PROs) and patient preferences. More concretely, the objectives of this study were to identify which decision-points can potentially include patient experience data, explore methodological considerations regarding PROs and patient preferences, and map current efforts on patient engagement, namely published guidance, and initiatives. An additional objective of this study was to review the literature on the use of PROs and patient preferences in multiple myeloma in order to report and discuss real examples of the contribution of such methods to better inform decision-making.

The study was guided by the following research questions:

1) What is patient experience data?
2) What methods are being used to capture patient experience data?
3) What are PROs and patient preferences?
4) What potential roles may PROs and patient preferences play in the MPLC?
5) How are such methodologies being used to inform decision-making?
6) What challenges do PROs and patient preferences face?
7) What guidelines are available to inform the use of PROs and patient preferences in decision-making throughout the MPLC?
8) Which initiatives are being undertaken to enhance the use of patient input in decision-making?
9) What distinguishes PROs from patient preferences?

3 Methods

A literature search was conducted on PubMed in December 2021. This work was framed by four sections: 1) overview of patient experience data, 2) PROs as a methodology for the collection and use of patient experience data in decision-making throughout the MPLC, 3) patient preferences as a methodology for the collection and use of patient experience data in decision-making throughout the MPLC, 4) and a case study on the use of PROs and patient preferences for the collection and use of patient experience data in multiple myeloma. Search queries were developed based on the study objectives and research questions and included free text terms in the title and abstract related to Patient Reported Outcomes and Patient Preferences in the context of medicines' life cycle. The search queries can be found in Appendix 2. Since this field is rapidly evolving, the literature search was repeated in August 2022 to identify eventual new literature, hence ensuring that no relevant studies were missing. Identified citations were downloaded into Mendeley reference management software.

Additionally, a Google search was conducted between January and August 2022 to identify grey literature published by regulatory agency websites, HTA agencies, professional societies, public-private working groups, and other relevant initiatives to identify current information and experiences on patient involvement research provided by these stakeholders.

Publications were deemed eligible if they met the following inclusion criteria: any type of document in order to be as comprehensive as possible (*e.g.*, regulatory documents, HTA reports, project or workshop reports, reviews, original research articles, books, and perspective articles) 1) reporting or discussing the use of PROs and/or patient preferences in decision-making throughout the MPLC 2) or examining trends, benefits and/or limitations of PROs and/or patient preferences. The following exclusion criteria were applied: 1) not written in English, 2) no full text available, 3) published before 2012 (so that selected documents reflect the state of the art regarding patient experience research), 4) literature reporting only the use of PROs or patient preferences to assess satisfaction with health care services, 5) and studies regarding the use of PROs or patient preferences in medical products other than medicines (*e.g.*, medical devices).

The screening process was conducted in two stages. First, the title and abstract of each of the identified articles and the table of contents or headings of grey literature were screened for relevance based on the selection criteria. Then, the full text of potentially relevant documents was reviewed against the same criteria to confirm the relevance of each document.

Reference lists from eligible articles were hand-searched to identify additional relevant publications. Newly identified publications were added to the initial list. After excluding duplicates, these publications were also screened for eligibility using the same process aforementioned.

4 Results and Discussion: Methodologies on The Collection and Use of Patient Experience Data in Medicines' Life Cycle

4.1 Clinical Outcomes Assessments

In order to use patient experience data for medicine's assessment, it is necessary to develop reliable and validated instruments that allow data collection directly from patients, which can then be used to provide a more robust measure of clinical outcomes. The relevance of these tools is that they offer a means for direct measurement of which clinical outcomes, patients find most relevant, and they are intended to determine, from multiple perspectives, whether a medicine shows clinical benefit (18).

The so-called clinical outcomes assessments (COAs) may be defined as an assessment of changes in how a patient feels, functions and survives and are divided into main four categories: patient-reported outcome (PRO), clinician-reported outcome (ClinRO), observer-reported outcome (ObsRO) and performance outcome (PerfO), as summarized below.

Patient-reported outcomes: according to the European Medicines Agency (EMA) "*any outcome evaluated directly by the patient himself and based on patient's perception of a disease and its treatment(s) is called patient-reported outcome (PRO). The term PRO is proposed as an umbrella term to cover both single dimension and multi-dimension measures of symptoms, health-related quality of life (HRQoL), health status, adherence to treatment, satisfaction with treatment, etc*." (18). This implies that the patient's experience is captured without modification or interpretation by a clinician, caretaker, or anyone else (18,19).

Health-Related Quality of Life (HRQL or HRQoL). Within this context, it is essential to mention a specific subset of PROs, HRQL. HRQL is a broad concept that is defined "*as the patient's subjective perception of the impact of his disease and its treatment(s) on his daily life; physical, psychological and social functioning and well-being*" (18,20). It has the underlying concept of multidimensionality, attempting to capture complex aspects of life which can change over time and are potentially influenced by the disease and/or treatment. Since it refers to a personal perspective, PRO data and particularly HRQL data, are also expected to vary with gender, experience, age, education and cultural background, disease stage, and treatment, among others factors (18,21). When an instrument is used to assess specific symptoms, it is

important to also consider the assessment of HRQL, in order to ensure that the positive impact on a symptom is not accompanied by an overall negative impact on HRQL (20).

A clinician-reported outcome is a measurement that comes from a healthcare professional, which observes the patient and makes a clinical judgement based on signs, behaviours and other manifestations related to the patient's health condition. It does not include symptoms, since these are only known to the patient and are therefore reported by the PRO (21).

An observer-reported outcome is a measurement of observable signs, events and behaviours related to the patient's health condition, which is neither done by the patient nor by a healthcare professional. It may come from a parent, caregiver or others involved in the patient's daily life and who are capable to describe these manifestations, mostly when the patient him/herself is not able to do so (21).

A performance outcome is a measurement based on a standardized task, performed by a patient according to a set of instructions, which is administered and evaluated either by a trained individual or by the patient independently. The performance of the patient of the given task is then extracted for the clinical outcomes assessment (21).

4.2 Patient-Reported Outcome Measures

PRO data are collected through PRO measures (PROMs)[1]. PROMs are standardized, validated tools or instruments (*e.g.*, questionnaires or diaries) completed as a self-report (18,20). According to EMA, PROMs include concepts best known to the patient or best measured directly by the patient (18,20). Therefore, PROMs may provide helpful information regarding subjective outcomes/concepts such as symptoms (*e.g.*, pain, fatigue, or nausea), mental functioning, physical functioning, well-being, adherence to treatment, satisfaction with treatment, and treatment preferences (19,20,22).

PROMs can be classified as generic or disease-specific. Generic PRO instruments can be used irrespectively of disease or patient and they aim to measure single or multidimensional health concepts such as cognitive function, performance status, symptoms, and pain. Further, generic PRO instruments can also be used in healthy people (*e.g.*, as part of a population or sample survey to evaluate overall health and well-being, or a nontreatment intervention study). Since

[1] PROMs and PRO instruments are considered synonym terms, and therefore, will be used interchangeably throughout this report.

they can apply to various patient populations, they enable comparison across different treatments or groups of patients under different environments/contexts and conditions (18,20,23). Nevertheless, generic PROMs lack sensitivity regarding relevant disease domains and can be less responsive to change when compared to disease-specific PROMs, hence underestimating health changes. Moreover, they may fail to capture relevant disease-specific concepts.

Disease-specific PRO instruments measure the impact of a specific disease. They may also capture some generic health domains/concepts, depending on their purpose, but are typically tailored to address particular features of a particular disease. Disease-specific PRO instruments tend to be of higher relevance and change responsiveness, providing more comprehensive information on specific aspects of a condition. On the other hand, they may not be able to capture unexpected adverse reactions, and they do not allow comparisons across different patient populations and distinct diseases or conditions. Finally, they are not easily incorporated into economic evaluations (18,19,23–26).

Table 3 summarizes the main advantages and disadvantages of generic and disease-specific PROMs and presents examples of each type of PROM.

Table 3. Generic and disease-specific instruments.

	Generic PRO instruments	**Disease-specific PRO instruments**
Advantages	Allow for comparison across distinct treatments or groups of patients. Allow for comparison with the general population data that can be used to interpret scores.	Tailored to a specific disease/condition. May have higher relevance and change responsiveness. May be more sensitive to particular domains of a disease.
Disadvantages	May include less relevant items, or on the contrary, exclude relevant items.	Do not allow for comparisons across patient populations with different diseases or conditions.

	May be less sensitive to changes within the specific domains of the disease.	May fail to identify relevant general domains and unexpected treatment-related toxicities. Do not allow for comparison with the general population data.
Examples (18,19,27)	EuroQoL-5 (EQ-5D); 36-Item Short Form Survey (SF-36); Nottingham Health Profile (NHP); and Sickness Impact Profile (SIP); Patient-Reported Outcomes Measurement Information System (PROMIS); World Health Organization Quality of Life-100 (WHOQOL-100); Visual Analogue Scale (VAS); 12-Item Short Form Survey (SF-12).	EORTC QLQ-C30 (European Organization for Research and Treatment); Functional Assessment of Cancer Therapy-General (FACT-G); International Index of Erectile Function (IIEF); National Eye Institute Visual Functioning Questionnaire; Paediatric Asthma Quality of Life Questionnaire (PAQLQ), Quality of Life in Epilepsy (QOLIE); Rotterdam Symptom Checklist (RSCL); Lung Cancer Symptom Scale (LCSS); MD Anderson Symptom Inventory (MDASI); Functional Assessment of Cancer Therapy Hepatobiliary Cancer Symptom Index - 8 Item Version (FHSI-8); Functional Assessment of Cancer Therapy - Ovarian Symptom Index (FOSI); Functional Assessment of Chronic Illness Therapy (FACIT); Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE).

PROMs can also focus on broader health conditions or states rather than specific diseases. These PRO instruments are generally used to assess a range of functional status or disability measures on particular population groups (*e.g.*, elderly, patients with mental health problems). Examples of this type of PROM include the Kessler-10 Psychological Distress Scale (K10), and the Functional Independence Measure (FIM) (24).

It is vital to select a PROM (generic or disease-specific) that is fit for purpose considering the study's objective(s) and the characteristics of the patient population (18). For example, and taking into consideration what was mentioned before, if the PROM is intended to be administered to healthy people or patients with several comorbidities, a generic PROM would be more likely appropriate. By contrast, when measuring outcomes related to a particular disease or treatment, a specific PROM would be preferable. Additionally, the outcomes and concept(s) of interest also inform which type of instrument to choose. Broader concepts, such as HRQL, are usually included in generic PROMs, whereas a specific PROM will measure the specific impact of a disease or treatment (23) but can also include HRQL measures.

Given the advantages and limitations of each type of PROM, some authors recommend the combined administration of generic and disease-specific PROMs for a more comprehensive evaluation (23). However, for example, the Australian Commission on Safety and Quality in Health Care has warned about measurement errors that may result from including both generic and specific items into a single instrument (24). As an effective alternative, hybrid measurement systems, also known as modular packages, use a generic health measure plus complementary disease-specific instrument(s). For example, PROMIS (Patient-Reported Outcomes Measurement Information System) consists of item banks for the evaluation of key health domains across common chronic diseases, broadly covering the relevant physical, emotional, and social domains of a given disease. The FACIT (Functional Assessment of Chronic Illness Therapy) system also comprises a generic HRQL measure and complementary disease-specific subscales. This modular approach may improve comparability of PRO data, which tends to be lacking in disease-specific PROMs. Since these modules are able to be measured and analysed separately, each of these modules can be assessed with different frequencies, thus minimizing respondent burden (23,24,27,28).

4.2.1 Applications of Patient-Reported Outcomes

As the patient's perspective is gaining increasing importance in the context of health care providers, researchers, regulators, along with other stakeholders, PROs for measuring and evaluating health outcomes have been rapidly recognized worldwide. Over time, PROs have been increasingly implemented in clinical practice, enhancing patient-centred care and clinical decision-making (19,22,29–31). Several studies have reviewed the value of PRO data to inform clinical research, payers/HTA bodies, regulatory and healthcare policy decisions, and some selected examples are depicted in Table 4.

Table 4. Recent studies on PROs used in the context of clinical trials and regulatory environment.

Examples	**Aim**	**Main findings**
Role of PRO and other efficacy endpoints in medicines' approval process in Europe. (32)	To review the role and extent of PRO use in EMA: European Public Assessment Reports (EPAR) between 2012 and 2018.	- PROs were used as endpoints in 46% of all medicinal products, of which only 37% had PROs as primary endpoints. - To increase transparency, the authors advise to always fully and clearly reporting all endpoints used.
PRO reporting in summaries of product characteristics (SmPCs) for new medicines. (33)	To investigate to what extent PROs used in clinical trials were included in SmPCs of new medicines in Germany from 2014 to July 2018.	- Of the 143 randomized clinical trials (RCTs) assessed, 109 (76.2%) included PRO data, of which 89 were included in the SmPCs. - 42.7% of the RCTs investigated antineoplastic agents, 20.2% anti-infectives (for HIV or chronic hepatitis C), and 37.1% other medicinal products. - For 50 of the 89 RCTs, the study population matched the target population specified in the SmPC.

		- Reporting of PRO data was poor for both oncology and infectious diseases, especially for the latter. - The study highlights the importance of PRO reporting in SmPCs to support informed decision-making in a patient-centred care.
PRO claims in European and United States for orphan medicines approvals. (34)	To evaluate the rate of usage and the kind of PRO claims in orphan medicines approvals from EMA and FDA between 2012 and 2016.	- The rate of PRO claims was lower for orphan medicines compared to the overall approvals conceded by the EMA. - Only 21.7% of the approvals presented PRO data in the respective SmPC, which was significantly less than what was reported for the overall new medicines' approvals by the EMA from 2008 to 2012 (46%). - The findings suggest EMA is more willing to grant PRO claims, including HRQL, when compared with the FDA.
A review of PRO labelling for oncology medicines approved by the FDA and the EMA. (35)	To compare PRO labelling for new cancer medicines approved by the EMA and the FDA for any indication between 2012 and 2016.	- 70.3% of approved oncology indications included PRO data in submission documents. - No indication received PRO labelling from the FDA, whereas EMA granted PRO labelling to 46.7% of all indications that had PRO data (and 32.8% of all indications reviewed). - The FDA and the EMA use different evidentiary standards to assess submitted PRO data from oncology studies. The authors identified areas of differences between agencies: study design, concepts

		assessed, measures used for assessment, missing data, and assessment schedules. - About 50% of the indications reviewed received PRO labelling by EMA based on open-label studies. The risk of bias associated with open-label studies needs to be considered. - Contrary to EMA, the FDA does not consider HRQL as a reliable concept for product labelling. - The study suggests that some PROMs currently used in oncology studies may be outdated and unsuitable for clinical trials.
A systematic review of HRQL assessment and reporting on oncology randomized phase III trials. (36)	To evaluate the inclusion of HRQL as an endpoint in cancer clinical trials in major journals between 2012 and 2016.	- The study found reporting deficiencies in terms of under-reporting and delay of publication. - Out of 231 primary publications of oncology randomized phase III trials with HRQL data as a secondary or exploratory endpoint, HRQL results were available in only 143 (61.9%). - Overall, 70 secondary HRQL publications were found: for clinical trials without HRQL results in the primary publication, the probability of secondary publication was 12.5%, 30.9%, and 40.3% after 1, 2, and 3 years, respectively. - Proportion of trials not reporting HRQL results was similar in trials with positive (36.5%) and with negative results (39.4%),

		but the probability of secondary publication was higher in positive trials.
A systematic review of the quality of statistical methods employed for analysing HRQL in cancer RCTs. (37)	To identify and characterise the quality of the statistical methods generally used for analysing HRQL data in cancer RCTs from 1991 to 2017.	- From the 33 RCTs assessed, missing data were common, with compliance rates from 45% to 90%. - 29 studies did not adequately adjust the data for the type I error. - Only 4 studies adequately analysed the missing data, therefore properly considering the informative nature of missing data.

4.2.1.1 Medicine Development and Approval

Medicine development has focused more on patient-centricity since it has been fully acknowledged that the patient's perspective can improve the quality, safety, and efficacy of medicines. On the other hand, new therapies increasingly aim to improve patients' quality of life and symptom management. Thus, international regulatory agencies have shown a growing interest in having PRO data from clinical trials in marketing authorization applications for new medicinal products (18,29,38).

From a regulatory perspective, PROs can provide added value throughout the medicine's lifecycle. Specifically, PRO data collected in clinical trials can inform the medicine development phase, approval and monitoring processes, benefit-risk assessment, and labelling claims (29).

PRO data can be included in a medical product labelling as safety and tolerability data and/or as a specific claim of treatment benefit. This can be relevant considering not only that the patients' have first-hand knowledge of the effects of a certain medicine, but also from the HTA perspective, given the rising treatment costs that render it essential to focus on what is perceived by the patients as clinically important and what addresses their needs (20,22,39). In fact, the patient's perspective can complement traditional endpoints (*i.e.,* objective clinical outcomes and laboratory parameters), since the latter may not always fully capture the impact of a treatment (either positive or negative effects). For instance, PRO data may help in disclosing treatment-related symptoms that need to be addressed or support the choice between two

medicines with a similar efficacy profile (40)**.** Several methodological guidelines have been developed to promote best methodological practices for the use of PRO in clinical trials. The "Patient-Reported Outcomes Tools: Engaging Users & Stakeholders" (PROTEUS) Consortium has identified core documents on designing PRO protocols (41), selecting PROM(s) (42), analysing PRO data (43), reporting PRO findings (44), among other aspects. These tools have been aggregated and described in detail in the PROTEUS Handbook. This document also includes a roadmap to obtaining high-quality PRO evidence using these PRO tools (45). Selected guidance documents/PRO tools are briefly described below.

The SPIRIT-PRO Extension (Standard Protocol Items: Recommendations for Interventional Trials in Patient-Reported Outcomes) was issued in 2018 and is a 16-item checklist on what specific PRO content should be included in protocols. It aims to improve the completeness and transparency of clinical trial protocols where PRO are primary or key secondary endpoints (41). The authors recommend using the SPIRIT-PRO Extension together with the SPIRIT 2013 Guidelines, which sets the minimum content for a clinical trial protocol. The SPIRIT initiative has further published a paper with detailed implementation instructions and a protocol template with examples from existing trial protocols to promote understanding of the guidelines and facilitate implementation (46).

In 2013, the International Society for Quality of Life Research (ISOQOL) published guidance on minimum standards for PROMs in patient-centred outcomes and comparative effectiveness research. These standards can inform the selection of PROMs for the respective research studies (42). In the same year, ISOQOL also developed a set of recommended standards for reporting RCT PRO results (47).

In 2021, the SISAQOL (Setting International Standards in Analysing Patient-Reported Outcomes and Quality of Life Endpoints Data) Consortium published preliminary recommendations for standardising the analysis and interpretation of PRO and quality of life data in cancer clinical trials. These recommendations intend to facilitate the development of international consensual standards for PRO analysis in cancer RCTs. The document focuses on developing a taxonomy of research objectives that can be matched with appropriate statistical methods, identifying suitable statistical methods for PRO analysis, standardising statistical terminology related to missing data, and determining appropriate ways to handle missing data (43).

The CONSORT-PRO Extension (Consolidated Standards of Reporting Trials Statement-PRO extension) was published in 2013 aiming to improve reporting of RCT PRO findings. It includes

a five-item checklist on what should be included when reporting RCTs in which PROs are primary or secondary endpoints: (1) PRO must be identified as primary or secondary outcomes in the abstract; (2) a description of the hypothesis of the PRO and relevant domains must be provided (*i.e.*, if a multidimensional PRO tool has been used); (3) evidence of the PRO instrument's validity and reliability must be provided or cited; (4) statistical approaches for dealing with missing data must be explicitly stated; and (5) PRO-specific limitations of study findings and generalizability of results to other populations and clinical practice must be discussed (44). Cappelleri *et al.* also suggested a "sixth criterion of explicitly stating the respondent definition or clinical important difference definition for each endpoint to aid in the interpretation of results" (19). Figure 2 presents a diagram that compiles the main resources to develop high-quality PRO trial design, analysis, and reporting.

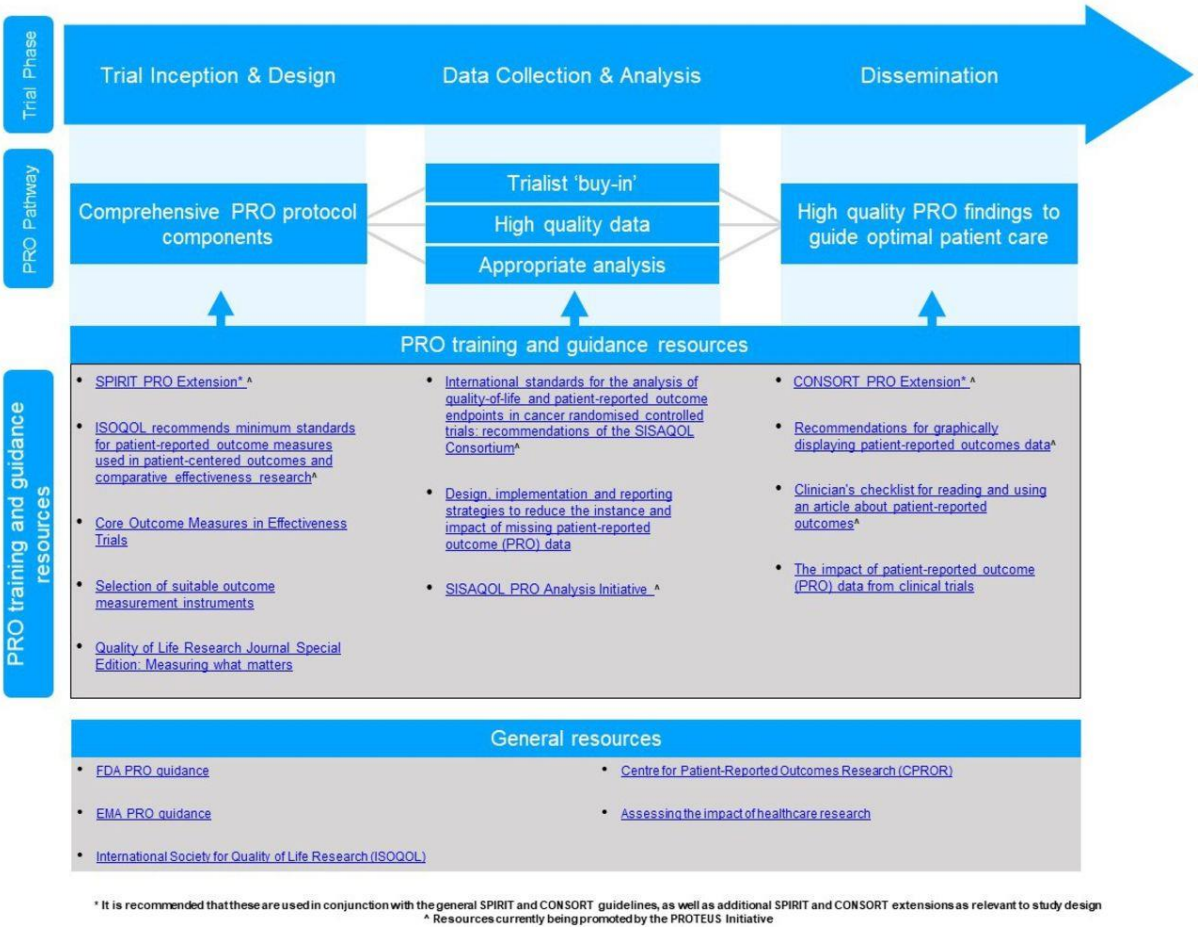

Figure 2. Resources to develop high-quality PRO trial design, analysis, and reporting. Retrieved from Calvert *et al.* (46).

4.2.1.2 Real-World Setting

Conventionally, PRO data are more often collected in clinical trials to support regulatory, HTA, and clinical decision-making. However, stakeholders are broadening their interest in better understanding the patient perspective in the real-world clinical care setting where PRO data collection has been of added value in providing information on the healthcare needs of the population and adding knowledge regarding the profile of a certain treatment (*e.g.*, PRO data may give rise to PRO alerts, provide long-term safety and effectiveness) (26,48). Furthermore, real-world PRO data can also inform the early stages of medicine development. By gathering insights on the natural history of the disease, disease burden, and unmet needs, researchers can select the most suitable endpoints for subsequent clinical trials. Finally, PROs may be a source of evidence in early access, compassionate use, and off-label use contexts. The real-world evidence generated may contribute to HTA, guideline development, and clinical and health policy decision-making (49).

Engel *et al.* reviewed all publicly available data on post-authorization safety studies (PASS) protocols submitted to the Pharmacovigilance Risk Assessment Committee (PRAC) from July 2012 to July 2015 and found that PRO use among regulatory medicines post-authorization assessment is still low. Almost half of the electronic register of post-authorization studies (EU-PAS) entries had the protocols available, of which only 14% included PRO data. PROMs selected included assessment of symptoms, the burden of disease, and quality of life (48).

Secondary data sources (*e.g.*, electronic health records (EHR), insurance claims, administrative sources, and existing registries) do not always capture the patient perspective. The routine collection of PRO for EHR, together with other health data (*e.g.*, laboratory, and clinic records) has the potential to enhance individual patient management, quality of care evaluations, research, and value-based and global population health care. A multidisciplinary team led by Johns Hopkins University and funded by the Patient-Centered Outcomes Research Institute (PCORI) has recently developed the "Users' Guide to Integrating PROs in Electronic Health Records" (25). This Guide provides a practical framework along with examples for administrators, clinicians, researchers, information technology (IT) professionals, and other stakeholders who aim to integrate PRO into their EHR. The research team formulated 11 key questions for integrating PRO in the EHR, and for each question, they outlined different approaches, described the respective advantages and disadvantages, and provided case examples. Each section also identified information gaps/research questions and useful resources. It does not present a one-size-fits-all solution but rather a number of the approaches

presented that may be applied in a given context after careful consideration, since many of the options are not mutually exclusive (25,50). Thereafter, members of the Users' Guide wrote an article presenting their 11 questions clustered into three thematic groups: planning, selection, and engagement, with a summary of each theme including the main considerations and takeaways (50). Horn *et al.* used these three thematic groups (informed by the Users' Guide) to develop and implement a large-scale PRO-EHR system within the orthopaedic surgery department at a large academic health centre where they highlighted the challenges and facilitators to implementing a PRO-EHR system and what future steps could be taken to improve response rate (51). Another noteworthy effort in this area is the work developed by Franklin *et al.* on the collection and use of PROMs in the learning healthcare system, which includes several considerations on the key steps to successfully integrate PROs in EHR (52).

4.2.1.3 Health Technology Assessment

A recent collaborative effort between the leading HTA networks, societies, and global organizations (including EUnetHTA, ISPOR and the World Health Organization), co-led by the International Network of Agencies for Health Technology Assessment (INAHTA) and Health Technology Assessment International (HTAi), led to the development of a new internationally consensual definition of HTA as "*a multidisciplinary process that uses explicit methods to determine the value of a health technology at different points in its lifecycle. The purpose is to inform decision-making in order to promote an equitable, efficient, and high-quality health system. Health technology assessment evaluates the consequences and impacts (e.g., medical, societal, ethical, and economic) of the application of health technology*." (53)

As previously stated, due to rising treatment costs, there is a growing acknowledgement of the need to complement safety and efficacy data with the patient's perspective to provide a more holistic assessment of benefit-risk assessments. Consequently, it is also necessary to progress toward a more patient-centric evaluation of health technologies (54,55). In other words, some authors argue that there should be a reframing of the concept of health value that includes what the patients perceive as value (*e.g.*, effectiveness, HRQL, direct and indirect cost) (55). In this sense, there is an opportunity to use PROMs in HTA to gather information on a treatment's added value, which, in turn, will affect market access, reimbursements, and pricing negotiations. Incorporating PRO data in HTA (along with differential clinical value assessed in clinical trials and estimates of change in direct healthcare costs) plays a key role in assessing

effectiveness and value assessment, and ultimately improves efficiency in resource allocation (54,56).

4.2.1.4 Clinical Care

PROs have been also contributing to a paradigm shift towards a more patient-centred care approach, which promotes patient empowerment with patients' active participation in treatment decisions (*i.e.*, shared decision-making). PROMs can be routinely incorporated in individual clinical care to assess treatment effectiveness, monitor outcomes over time, guide clinical decisions (*e.g.*, choosing from multiple treatment options), and enhance communication between patients and healthcare providers. Furthermore, PROMs are being applied to evaluate the quality of care/healthcare services (33). The ISOQOL has developed a guidance document regarding the implementation of PROMs in clinical practice (24,31,57).

Importantly, when PRO results are shared through a high-reach medium (*e.g.*, publication in peer-reviewed journals or reported in scientific/medical conferences), this information is more easily accessible to prescribers, patients, and patient advocacy groups. Consequently, on an individual level, PRO data may be vital for patients to make an informed decision on a given medicine (26).

4.2.2 Patient-Reported Outcomes Instrument's Characteristics and Conceptual Framework

As previously mentioned, a PRO is an outcome measured directly by the patient, based on his/her own perception of a disease and/or its treatment, which must be free from any kind of influence from others. To be valid and thus useful for medicine's assessment, this information from patients must be captured through robust instruments or tools, which include standardized information collection procedures, as well as guidance on implementation, and defined methods for scoring, analysing, and interpreting responses. In short, a PROM can be defined as an instrument or tool, specifically developed to guarantee a valid and reliable measurement of a PRO (18).

In order to trustworthily collect PROs, a PROM must comprise certain aspects that allow the information gathering from the patient, without interference from medical figures or others.

This information might be obtained through a questionnaire, a self-report, or an interview, among others. In either case, only the patient's answers are considered (18).

Through these instruments, depending on how they are built and what their purpose is, PROs can be obtained on the patient's functional status, HRQL, symptoms and symptom burden, personal experience of care, and other behaviours that are consequences of their health status or treatments (58). As mentioned previously, PROMs can be either disease-specific, if they are developed specifically to collect information for one disease, or they can be more generic, examining for example the cost of a health intervention (58).

The development of a PRO instrument should begin with the construction of a conceptual framework. A conceptual framework consists of an explicit description or diagram that presents the presumed relationships between the single items[2] (*e.g.*, difficulty walking), domains[3] (*e.g.*, physical impairment), and the overall concept(s)[4] (*e.g.*, activity impairment) measured and the scores produced by the PRO instrument. In other words, it describes how the simpler concepts can be properly clustered into the respective more complex concepts being measured. It should be noted that the domains – comprised of a respective group of individual items – although related, represent separate concepts (*e.g.*, the psychological function would be the broader concept comprising two related but distinct domains, emotional function, and cognitive function) (19,59).

The conceptual framework starts from the desired claim (or other purposes that motivates PRO assessment), and it should be developed based on literature review and experts, physicians, and patients' knowledge of the concept of interest. This framework will provide the rationale regarding what outcomes to measure and how this is to be accomplished. It should also determine the intended population and research application (*i.e.*, the purpose it should fulfil), which will, in turn, define the instrument's characteristics (*e.g.*, format, mode and frequency of administration, and maximum time required for completion) (60–62).

---

[2] An item is defined by the FDA as "*an individual question, statement, or task (and its standardized response options) that is evaluated by the patient to address a particular concept*." (59)

[3] According to the FDA, a domain is "*a sub concept represented by a score of an instrument that measures a larger concept comprised of multiple domains. For example, psychological function is the larger concept containing the domains subdivided into items describing emotional function and cognitive function*." (59)

[4] As defined by the FDA, a concept is "*the specific measurement goal (i.e., the thing that is to be measured by a PRO instrument). In clinical trials, a PRO instrument can be used to measure the effect of a medical intervention on one or more concepts. PRO concepts represent aspects of how patients function or feel related to a health condition or its treatment*." (59)

The PRO instrument should be based on a sound conceptual framework aligned with the research objectives to ensure appropriate measurement of the concept of interest, and ultimately justify its use to support a therapeutic claim (30). An inadequate conceptual framework may result in an unclear grouping, and ambiguity about what is being measured and what the scoring represents, therefore hampering analysis, interpretation, and the quality of findings. If the relationship between concepts is not well established, it will likely be intricate to understand what is effectively being measured and what a certain score represents (61,62).

A well-defined conceptual framework should also present outcomes that are relevant to the patients. For that reason, after the conceptual framework is hypothesized and throughout the instrument development process, patient input is vital to adapt and confirm the conceptual framework (*e.g.*, through conducting exploratory patient interviews, focus groups, and qualitative cognitive interviewing) (59,60,63).

Importantly, the framework is expected to evolve as evidence is gathered over the course of the instrument's initial development. The final conceptual framework should stem from patient input and measurement property testing, which will confirm, prior to the creation of the instrument itself, that the findings drawn from the application of the PRO instrument are valid and relevant (59,63).

4.2.3 Patient-Reported Outcomes Study Endpoints and Endpoint Model

A study endpoint corresponds to the measurement that will be compared across treatment groups to assess the effect of such treatment; thus it should be aligned with the study objectives, design, and data analysis. Only primary or secondary endpoints can be used in clinical trials to support labelling clams. A primary endpoint is the one of greatest relevance for the study (although there may be more than one primary endpoint, where in that case they are called co-primary endpoints), thus providing the best evidence of a treatment's benefit. The primary endpoint will essentially determine if the study meets its objective(s). PRO outcomes are more often secondary endpoints, which provide supporting evidence about the efficacy of a treatment or additional outcomes (considered of lesser importance) (64,65).

The PRO endpoint(s) should naturally have plausible relation with other PRO and non-PRO endpoints being used. Therefore, it is necessary to develop an endpoint model, a diagram that depicts the hierarchy of all the endpoints intended to support a claim. It should clearly state the PRO endpoint role, *i.e.*, primary, key secondary, or exploratory endpoint (59).

4.2.4 Patient-Reported Outcomes Measurement Properties

Given the importance of the information collected from PROMs, among the aspects already discussed, one must have into consideration the measurement properties that must be fulfilled when developing a PROM. To be useful to decision-makers (*e.g.*, regulatory agencies, HTA/payers, clinicians, researchers) and patients, a PRO must undergo a validation process to confirm that it measures what it is intended to measure in a reliable and accurate manner. To prove its validity, robust evidence should be gathered demonstrating that the instrument measures its purpose and that the items and domains of the instrument are appropriate and comprehensive regarding its intended measurement concept, population, and use (58).

Content validity can be defined as the extent to which an instrument measures the concept of interest that it was designed to measure. When it comes to a PRO instrument, qualitative work with patients is relevant since a PRO is meant to measure the important concepts from the patient's point of view. This way, the PROM should be built according to the patient's comprehensiveness and perspective, and not according to clinicians and other stakeholders. The content validity is put at stake if, for example, the conceptual framework of the PRO and its claim are not aligned. A component of validity is **criterion validity**, which intends to describe how the score of a particular instrument used relates to a gold standard. It is an estimate of how similar the instrument used is to the gold standard instrument. (45,66).

Construct validity is established as the extent to which a score given through one instrument matches consistently with the hypothesis established, regarding the claims being measured, and represents the relationship between the score and the theoretical claim. For example, if a questionnaire is developed as a PROM to evaluate how one disease/therapeutic causes breathlessness, the construct validity of this instrument would be the extent to which it would measure breathlessness, instead of anxiety or shallow breathing, or any other situations that could be mistaken with the actual claim it is intended to measure (45,58,66).

An instrument must also show **reliability**, a measurement property that also contributes to its validity. Reliability means that the instrument will reproduce consistent results over time, if applied at different time points, for example throughout a clinical trial (45,66,67).

A PROM should also be **able to detect if clinically important changes** have occurred in an outcome. The degree to which a PROM can detect the changes in the measures over time should be well defined in advance. Another relevant measurement property of the PROM is the **minimal important clinical difference** or **minimal important change**, which can be defined

as a measure of the smallest change in an outcome that patients perceive as important and may therefore require a change in patients' management (66).

4.2.5 Patient-Reported Outcomes Challenges

Several challenges have been reported in recent studies concerning PROM study design, implementation, reporting, and interpretation, which have hindered the regulatory use of PRO data (28,57). Selecting the appropriate PRO as an endpoint and the most suitable instrument to support medicine approval is a challenging task, especially considering the multitude of PRO instruments available. This includes deciding whether to use a disease-specific or a general PROM as discussed above. Although several validated PRO instruments are available to collect PRO data, significant barriers persist in successfully incorporating PROMs into regulatory practice (68).

Over the last decades, methodological obstacles and flaws have been reported to reduce the impact of PRO data on regulatory decisions (20). Regulatory bodies recommend a systematic assessment of a core set of PROs using fit-for-purpose PRO instruments. However, no standard method for collecting, analysing, or interpreting PRO data in clinical trials is yet available (20,28). This lack of standardization hinders the quality of PRO data and makes it difficult to compare results across various clinical trials (38,69,70).

There are also hurdles at the level of study design to overcome. For instance, PRO objectives are often poorly defined and there are concerns regarding open-label and single-arm trial designs (18,29,71,72). Although only randomized, double-blind clinical trials are recommended to avoid bias, some authors argue that open-label and single-arm trials may nevertheless be informative whenever the former trial design is not feasible (20,67). A further challenge is defining the optimal timing and frequency of assessments (70). For example, it will depend on the natural course of the disease, how a given medicine is administered (*i.e.*, route of administration and posology), and the recall period (28,67). If the recall period is too long, some important events may be missed (*i.e.*, the respondent may not be able to accurately recall the information), therefore introducing information bias. Shorter recall periods will minimize recall bias, but might be unsuitable when assessing infrequent activities (*e.g.*, walking a long distance) and should be carefully considered to not overburden participants, administrators, and resources (67,73).

Participant burden is also a complex issue since it depends not only on the frequency and timing of PRO assessment, but also on the trial duration, length and/or formatting of the instrument, mode of administration (*e.g.*, paper, telephone- or web-based), literacy level, the complexity of instructions, and disease severity and/or treatment toxicity (*e.g.*, if the patient is too sick to complete questionnaires) (67,74). An excessive respondent burden may result in unwillingness to complete the questionnaires and, ultimately, will result in missing data. Therefore, extensive and time-consuming surveys are generally unpractical for clinical use (74). The challenge is to obtain a balanced PRO instrument in terms of comprehensiveness and length, able to capture all the important aspects in a concise manner (74). It is crucial to keep in mind that the need/benefits from the PRO assessment should always outweigh the associated burden and that patient input should be sought to inform the burden acceptability from their perspective (23,75).

Electronic PROs (ePROs) have been reported as a potential solution to streamline PRO assessment, analysis, and presentation. Electronic methods for collecting PRO data (including computers, smartphones, and tablets) can enhance PRO data collection, storage, and interpretation, in a faster and cheaper way (46,74,76). Moreover, web-based PROMs enable real-time assessment, either inside or outside of a healthcare facility, and may allow an effective longitudinal measurement (PRO follow-up) (23,51,67,74). Cella *et al.* have identified two pilot studies conducted among patients with advanced lung cancer where computer technology was successfully used among patients and physicians (23). Nevertheless, this collection method may not be suitable for specific patient groups, such as elderly patients, for which alternative administration modes have to be used, such as telephone-based interactive voice-response systems (20,47,77). Computerised adaptive testing has the potential to identify a smaller subset of questions from the entire instrument for each patient, still accurately predicting the corresponding score (72,74). For example, PROMIS items have been used for computerized adaptive testing to minimize patient burden (57).

Missing data is a well-known methodological problem in PRO analysis, which is defined by the SISAQOL Consortium as any "*data that would be meaningful for the analysis of a given research objective or estimate, but were not collected*" (43). The study protocol should describe how missing data will be handled in the analysis (*e.g.*, use of imputation methods, sensitivity analysis). The proportion and reasons for missing values should also be reported (*e.g.*, disease progression with difficulty in completing questionnaires, death, treatment toxicity, and patient or clinician decision). For example, if only patients who feel better are able to complete the questionnaire, it will likely introduce selection bias, resulting in misleading results (43,70).

Tykodi *et al.* have also pointed out that the high rate of missing data is due to the logistical difficulty and time-consuming implementation of PRO assessment in clinical trials, which is why it is often deprioritized (77). Efforts should be made to achieve a high response rate even in special patient populations (*e.g.*, young, elder, or sick patients, and/or patients with low literacy)(76).

To overcome the barriers associated with missing data and improve completion rates, several recommendations have been provided, including: assuring that patients understand the purpose of the assessment and value the utility of PRO data; giving clear instructions to participants, and ensuring that physicians are also aware of the value of PROs and receive training on the collection and interpretation of PRO data; assigning a person responsible for PRO data collection in a given study, checking for completeness of questionnaires, and ascertaining the reasons for missing values (20,31,77,78). The SISAQOL Consortium has issued a set of recommendations on how to manage missing data (43).

Other barriers relate to the nature of PRO, for example, inherent patient-to-patient variability (18,38). Although PRO data may potentially lead to a range of benefits in patient care, according to a recent systematic review conducted by Rivera *et al.*, it is difficult to measure direct and indirect PRO impact, and appropriate impact metrics are not well defined (78). Furthermore, interpretation of PRO data is hindered by the difficulty in isolating symptomatic side effects from disease-related symptoms and by the lack of consensus on what degree of difference is clinically relevant (20,72). Finally, translation and cultural adaption of PROMs are vital for assessing a wider population (*e.g.*, multicentre, and multinational clinical trials) and to obtain results with less risk of bias and increased external validity. However, cultural and language adaptations pose challenges because of the inherent ambiguity of language that may lead to incorrect interpretation and potential sensitivity of some questions or concepts across different cultures (26,58,74,76).

Specific conditions impose additional challenges. For instance, there are a limited number of PRO instruments available specifically for rare diseases. Besides, developing a new PRO instrument is an even more arduous process due to the small, heterogeneous, and often geographically dispersed patient populations (67,74). In cancer clinical trials, the overlap between symptomatic side effects and disease-related symptoms is much more pronounced (*e.g.*, ascertaining if anorexia is related to the disease or the treatment) (29,79) and some PRO instruments are outdated for assessing adverse events related to new therapies, such is the case with immune-based therapies (35,77).

All the challenges previously mentioned may reduce the potential for PRO data. This raises ethical concerns regarding the waste of limited resources, patients' efforts, and research (78). To overcome these barriers, there is consensus on the need for international collaboration in order to develop harmonized methodological guidelines.

4.2.6 Relevant Guidance and Other Documents on Patient Reported Outcomes

Extensive collaborative multi-stakeholder efforts are required to improve and harmonize PRO. Regulatory agencies, namely the EMA and the FDA are engaging in efforts to create guidelines and define best practices with respect to the use of PROs for medicines' regulatory assessment.

4.2.6.1 EMA Guidance Documents

Reflection Paper on the Regulatory Guidance for the Use of Health-Related Quality of Life (HRQL) Measures in the Evaluation of Medicinal Products (July 2005) (40).

This Reflection Paper aims to discuss the role of HRQL in the medicine development process. While not conceived as a guidance document, it provides broad recommendations on the use of HRQL in clinical trials to support label claims. This document applies only to HRQL and not to other PROs. It also provides brief considerations about study design and statistical analysis in the context of HRQL assessment. Finally, the paper presents additional recommendations such as particular conditions in which HRQL data may be of greater value (*e.g.*, life-threatening diseases like cancer).

Qualification of Novel Methodologies for Medicine Development: Guidance to Applicants (January 2009, updated 2014) (80).

The EMA has provided guidance on the qualification process for medicine development tools (DDT). This guidance describes the process for sponsors and researchers to obtain DDT qualification expeditiously, which is also applicable to novel PROMs. The ultimate objective is to develop DDTs that can help streamline the medicine development process, increase the chances for clinical trial success, and generate more comprehensive knowledge about a given disease and/or treatment. EMA reviewers will guide and counsel the DDT development process,

which in turn will assure the agency that a particular DDT will be appropriate for the qualified purpose without needing to reconfirm the DDT's utility during medicine development (19,80). There is also a specific *Questions and Answers* document on the qualification of digital technology-based methodologies to support the approval of medicinal products.

Appendix 2 to the Guideline on the Evaluation of Anticancer Medicinal Products in Man: The Use of Patient-reported Outcome (PRO) Measures in Oncology Studies (April 2016) (18).

This appendix results from the maturation of a reflection paper first published in 2014 - "Reflection Paper on the use of patient-reported outcome (PRO) measures in oncology studies". The appendix issued in 2016 focuses on the use of PROs (and HRQL) in oncology studies from a regulatory perspective. This guidance covers general aspects concerning the collection of PRO data in oncology studies, featuring specific sections about study design, and relevant concepts such as clinically important differences and added value. The document's intent is to reflect on the principles of scientific best practice rather than to provide specific recommendations regarding PRO validation, selection, or application. Therefore, while this paper focuses on oncology, it also addresses issues common to all trial research (*e.g.*, PRO endpoints). In essence, this appendix aims to encourage developments in the methods and application of PROs in the oncology regulatory setting (18).

4.2.6.2 FDA Guidance Documents

Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labelling Claims. Guidance for Industry (December 2009) (59).

This guidance provides considerations on PRO instrument development and trial design for labelling claims. It describes how the FDA reviews and evaluates the suitability of PROMs and specifies the appropriate scientific evidence and supporting documentation required for a PROM intended to support regulatory approval and labelling claims. The agency highlights that this guidance should be deemed only as recommendations rather than as regulatory requirements, unless otherwise stated. The document emphasizes the following concepts: conceptual framework, endpoint model, and content validity. Furthermore, it describes the measurement properties, namely reliability, validity, and ability to detect change. Additional notes are presented regarding the selection, modification, and development of a PROM, as well

as study design, data analysis, ePRO instruments, and the importance of including patient input during PROM development (59).

Roadmap to Patient-Focused Outcome Measurement in Clinical Trials (August 2015) (81).

The Division of Clinical Outcome Assessment published the *FDA Roadmap to Patient-Focused Outcome Measurement in Clinical Trials* to help researchers develop new or adapt existing tools, including PROMs, that measure outcomes that matter most to patients (81).

Qualification Process for Drug Development Tools (October 2020) (82).

Like the EMA, the FDA also has issued the final guidance on the qualification process for DDTs in the United States, including PROMs. This guidance describes the process for sponsors and researchers to obtain the qualification of novel DDTs from the Agency. Once qualified, DDTs will be available to be applied in any medicines development program for the qualified context of use without needing FDA to reconsider and reconfirm their suitability. Increasing public availability of qualified DDTs for a specific context of use will help optimize medicines development and facilitate the regulatory review, enabling earlier access to medical therapies. All information on the DDT qualification project, including FDA's decision to accept or not accept the submission, and FDA's recommendations on further DDT development, are publicly available on FDA's website and are updated on a biannual basis. (82)

Patient-Focused Drug Development (PFDD) Initiative

FDA is currently developing a series of four methodological PFDD guidance documents to address how stakeholders can collect and submit robust and relevant patient experience data for medicines development and evaluation (83). Table 5 describes the scope of each of the four guidance.

Table 5. Summary of FDA's Patient-Focused Drug Development Guidance Series for Enhancing the Incorporation of the Patient's Voice in Medical Product Development and Regulatory Decision Making

FDA Guidance	**Scope**
PFDD Guidance 1: Collecting Comprehensive and Representative Input (Final guidance – 2020) (5)	Sampling methods for patient data collection. Overview of the relation between research question(s) and patient data collection method(s), to aid the decision from whom to collect data.
PDFF Guidance 2: Methods to Identify What is Important to Patients (Final guidance – 2022) (16)	Methods for collecting patient data, in order to gather relevant information for patients on symptoms, and impacts of their condition, among other relevant aspects. Best practices for conducting qualitative research (*e.g.*, conducting and planning for interviews, or selecting types of survey questions) Survey methods and qualitative research aspects to consider in order to prevent biased results
PFDD Guidance 3: Selecting, Developing or Modifying Fit-for-Purpose Clinical Outcomes Assessments (in development) (67)	Approaches to selecting, modifying, developing, and validating COAs (including PROMs).
PFDD Guidance 4: Incorporating Clinical Outcome Assessments into Endpoints for Regulatory Decision-making (in development) (84)	Methodologies, standards, and technologies to collect, store and analyse COA data (including Pro data). Methods to incorporate COAs (including PROs) as robust and regulatory relevant endpoints for regulatory decision-making, namely: methods to define meaningful change and interpret results. Information on the format and content of COA data (including PRO data) required for regulatory submissions.

Core Patient-Reported Outcomes in Cancer Clinical Trials: Draft Guidance for Industry (June 2021) (28).

This document complements previous guidance on the use of PROMs in clinical trials by providing additional considerations specific to the cancer clinical trial setting. It provides recommendations on collecting a core set of PROs in clinical trials. Systematically assessing a core set of PROs using fit-for-purpose PROMs can minimize the existing heterogeneity in PRO assessment strategies, thus reinforcing the utility of PRO data. This guidance also covers considerations for instrument selection and trial design, namely recommendations regarding assessment frequency and strategies to mitigate missing data. Moreover, it provides some considerations on how PRO data can be included in the product label (28).

4.3 Patient-Preference Information

4.3.1 Patient Preferences: Scope and Definition

Multiple stakeholders, including the pharmaceutical industry, regulators, HTA bodies, payers, academia, clinicians, and patient organizations are increasingly exploring the value of another type of patient input, namely patient preferences, as an attempt to support the alignment between medicines development/regulatory decision-making and patients' values and needs (9,85–87).

Patient preferences are referred by the FDA as "*a statement of the relative desirability or acceptability to patients of specified alternatives or choices among outcomes or other attributes that differ among alternative health interventions*" (5). In this sense, patient preferences can be used to identify and quantify the relative importance of benefits and risks of treatment options from the patients' perspective. Ultimately, it can help to better understand the patient's willingness to trade-off between risks and benefits regarding a given treatment (or to determine the maximum acceptable risk for a given benefit; or on the contrary, the minimum required benefit for a given risk) (8,88). Once more, the patient's perspective is vital since they are the ones who are directly experiencing the disease and its treatment(s) and likewise, their value of benefits and risks may differ from that of decision-makers (*e.g.*, patients might be willing to accept more risk or less benefit than expected by the regulators) (9,85,89).

Patient preferences information may be most valuable in preference-sensitive decisions, which according to the Medical Device Innovation Consortium, are decisions "*in which there are multiple diagnostic or treatment options, and the decision which option to pursue depends upon the particular preferences of the decision-maker*". This includes the following situations (90):

- Multiple treatment options are available but there is no option that is clearly superior for all patients (*e.g.,* the benefit-risk trade-off is marginal, *i.e.*, "close calls");
- The evidence favouring one option above others is uncertain or variable;
- When there is preference heterogeneity, *i.e.*, patients' views about the most important benefits and acceptable risks of treatment differ significantly among patients, or from those of healthcare professionals and decision makers;
- When there is a need to understand patients' acceptability for uncertainty regarding treatments (*e.g.,* regarding long-term risks);
- Lifesaving treatments that entail high risks;
- Medical products that have temporal trade-offs (*e.g.*, early benefits with harms occurring later in time or vice-versa);
- Medical products that have substantially different benefits and/or risks compared with the available treatment alternatives;
- When there is a complex benefit-risk trade-off;
- When there is a high level of uncertainty concerning the benefit-risk profile (*e.g.*, a medical product unfamiliar to decision-makers or with novel technologies);
- When there is a perceived discrepancy between the views of patients and decision-makers.

Of note, patient preference elicitation is not necessary for every medical product and/or every decision across the medical product life cycle. Nevertheless, it can be useful in situations that require more complex decisions. For example, Figure 3 depicts the value of patient preferences according to different benefit-risk scenarios with varying complexities.

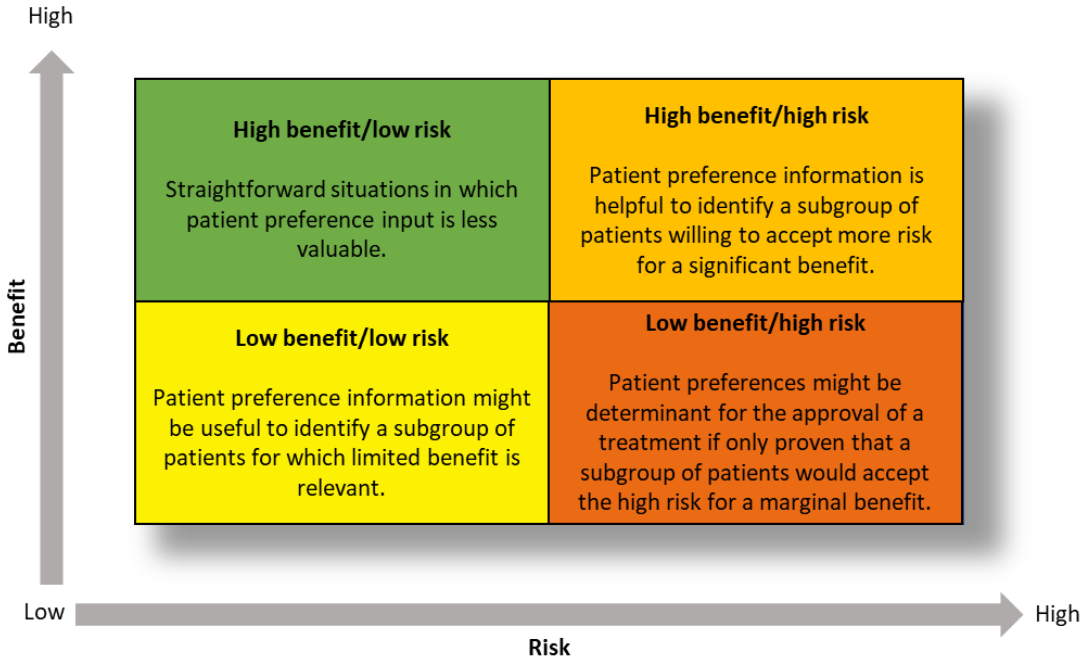

Figure 3. The value of patient preference information as a function of benefit and risk. Adapted from Ho *et al*. (89).

Following the same rationale as for PROs, patient preference information may complement traditional safety and efficacy data, ensuring that patients' preferences, needs, and values will guide decision-making. Therefore, patient preferences information can generate meaningful and valid results, leading to more informed and transparent decisions among regulators and HTA bodies. In turn, it is anticipated that patient-centred decisions will be more trusted by patients, clinicians, and the general public. Finally, such decisions might increase patient satisfaction, by meeting their needs and expectations, and ultimately improve their adherence to the treatment, leading to better health outcomes (and other non-health outcomes). By contrast and for certain situations, not including patient preferences in the decision-making process could result in increased costs due to the development of potential ineffective/irrelevant medicines that will not be approved, reimbursed, or that will lead to poor adherence to treatment owing to poor acceptability from patients (8,9,91).

There is a lack of understanding among stakeholders about how to incorporate patient preferences information in the medical product life cycle. Guidance is just now emerging, but it is not clear yet how much impact patient preferences have or will have on decision making, in which applications and stages of the medical product life cycle are patient preferences most valuable, or how they should be assessed. Therefore, patient preference information is currently

not effectively included in the decision-making process. While the experience in conducting and assessing patient preference studies is still limited, patient preference information is recognized as valuable input and several initiatives have been led to enhance patient-centric decision-making (8,9,87,92).

An important concept is patient preference heterogeneity, which may inform regulators and other stakeholders on how patients make benefit-risk trade-offs and which factors influence their decisions for a given situation. Patient preferences may vary according to disease characteristics or stage/severity, alternative treatment options, individual expectations, and tolerance, and sociodemographic characteristics (*e.g.*, age, employment status, education level, family circumstances, income, or ethnicity) (88,89,93,94). Therefore, since patients' perspectives on benefits and risks may be very heterogeneous within a patient group, collecting patient preferences information could lead to the approval of a novel treatment to only a subgroup of patients for which a given treatment is acceptable, thereby improving the effectiveness of those medical products (8).

4.3.2 Patient Preferences Methods

Patient preference information can be collected through both qualitative and quantitative methods. Qualitative methods are used to explore patient preferences while quantitative methods are used to elicit patient preferences. Preference exploration methods collect in-depth descriptive data about patient experiences, perspectives, and the treatment attributes that are most important to them. Qualitative research is usually unstructured or semi-structured, such as individual interviews, focus groups, and open-ended survey questions (4,90). In turn, patient preference elicitation methods quantify patient preferences in a structured manner. They collect numerical data that assesses the relative weights assigned to different attributes and what trade-offs are patients willing to make, allowing for statistical analysis and detection of preference heterogeneity. Examples of preference elicitation methods include discrete choice experiments (DCEs), swing-weighting, threshold technique, and best-worst scaling (BWS) (9,89,95).

A brief discussion will be further presented regarding the most popular elicitation method, DCEs. A more in-depth discussion on this and other elicitation methods can be found in recent publications (90,96,97).

Although methods can be classified as exploration or elicitation methods, they can also be classified as revealed preferences or stated preferences. Revealed-preference methods rely on

the observation of actual choices and behaviours in the real-world setting. Examples of revealed-preference methods include patient-preference trials and direct questions in clinical trials. Conversely, in stated-preference methods, patient preferences are elicited through hypothetical experiments. Stated-preference methods include direct assessment questions, discrete-choice experiments, threshold technique, conjoint analysis, and BWS (90,95,98).

Most patient preference studies in healthcare research use stated-preference methods. Revealed-preference methods are only possible for existing products in the market and thus are not applicable to novel medicines that are not yet available. Due to the hypothetical nature of stated preferences, it has to be assumed that patients would actually choose the options they say they would. While revealed preferences can avoid hypothetical biases, they still are subject to other bias, such as individual financial considerations. Furthermore, revealed-preference methods often are unable to infer the relative weights of individual attributes (88,90,98).

4.3.2.1 Discrete Choice Experiments (DCE)

DCE can quantify the relative weight of different attributes (*e.g.*, treatment characteristics or outcome) and assess the trade-offs patients are willing to make between benefits and risks. This method is used to explain or predict a choice from a set of discrete (*i.e.*, distinct/separable, and mutually exclusive) alternatives (86,95,99,100).

In DCE, the attributes of each treatment alternative are assigned different levels that are combined into profiles, which in turn are combined into groups of profiles referred to as choice sets. In other words, each attribute can take a range of levels, and different profiles result from the combination of those attributes with varying levels (*e.g.*, an attribute could be treatment duration with levels ranging from 1 week to 4 weeks) (1,90,97). Table 6 presents an example of a choice set of two hypothetical treatment profiles.

Table 6. Example of a hypothetical DCE choice set. Adapted from Myeloma UK and National Institute for Health and Care Excellence (95).

Attribute	**Option A**	**Option B**
Effectiveness	50% reduction of symptoms	80% reduction of symptoms
Treatment duration	1 week	4 weeks
Dosage regimen	Daily pill	Pill twice a day
Side effects	Mild headache	Moderate headache

In this survey-based approach, patients are presented with a choice set of two or more hypothetical treatment profiles and are asked to choose their preferred option, based on the attributes and their respective levels. There may also be an "opt-out" option which allows the patient not to choose any alternative if neither are acceptable, providing a more accurate picture of the expected uptake of that treatment. This task is then repeated over multiple choice sets. Finally, the resulting pattern of answers is analysed to estimate the relative contribution of each attribute level when opting for a given alternative and to infer the extent to which a patient trades off between attributes (1,99–101).

This method is useful not only to assess the relative importance of treatment attributes, but also to measure the maximum level of risk that a patient would be willing to accept in exchange for a given level of benefit, or the minimum level of benefit that would be required to accept a given risk. If out-of-pocket cost is included as an attribute, it is also possible to quantify the marginal economic/monetary value to patients of changes in attribute levels or the economic value of a treatment when compared to an alternative. At last, DCE can identify preference heterogeneity and investigate the characteristics of patients responsible for such discrepancies (*e.g.*, sociodemographic characteristics) that may explain their choice differences (1).

Various authors have identified DCE as the most used approach and it is perceived as the gold standard for eliciting patient preferences, due to its robustness and similarity to real-life decisions. Even the Innovative Medicines Initiative PROTECT project (Pharmacoepidemiological Research on Outcomes of Therapeutics by a European ConsorTium) has recommended DCE as the preferred method for patient preference elicitation (8,86,95). Moreover, there is now evidence that DCE can be used for eliciting patient preferences to inform regulatory benefit-risk assessments and support HTA and payer decisions

(1,86,99,100). However, it is not a 'one-size-fits-all' solution. For example, it is not a suitable method when there are many attributes to consider when patients cannot process a large amount of information or require approaches of easier comprehension, or in case of small samples which do not allow valid statistical analysis (*e.g.*, rare diseases) (14,95).

DCE strengths comprise the following: it is a common method with a solid theoretical base and established good research practices, training is available, and explores trade-offs across attributes. Despite these advantages, DCE also presents some limitations, such as being relatively burdensome and complex for patients, the difficulty to construct experimental designs to determine choice sets, and the often need to use specialist software for statistical analysis (97).

4.3.3 Applications of Patient Preferences

Although its current use is limited, several studies have identified potential roles of patient preferences throughout the MPLC. The main decision points throughout the MPLC in which patient preference may yield useful information are outlined in Figure 4. Table 7 presents some examples of studies that used patient preference information in benefit-risk assessment and regulatory decision-making.

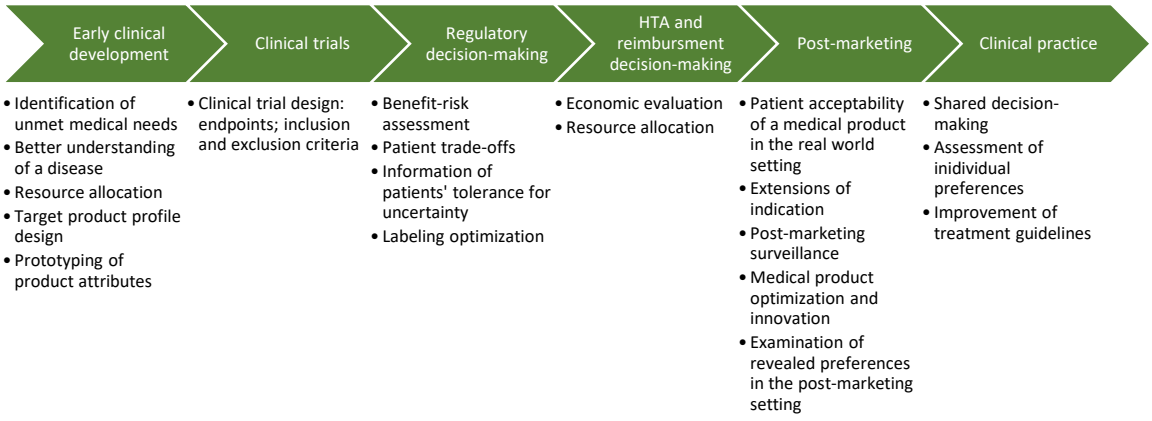

Figure 4. Applications of patient preferences along the medical product life cycle. Adapted from Innovative Medicines Initiatives & van Overbeeke *et al*. (1,9).

Table 7. Recent studies on patient preferences used in the regulatory setting.

Examples	**Aim**	**Main Findings**
Benefit-risk assessment using patient preferences for antiepileptic medicines (99)	To investigate the impact of eliciting benefit-risk preferences using DCEs. To demonstrate how patient preferences elicitation can be incorporated in benefit-risk assessment.	- Patient preference elicitation, in addition to clinical data, could lead to different treatment choices or regulatory decisions (*e.g.*, women with the potential to become pregnant prefer lamotrigine over valproate, due to the risk of teratogenicity associated with valproate, despite clinical trial results showing valproate to be significantly more effective than lamotrigine in generalized onset seizures). - The study presents a transparent and valid approach to investigating patient preferences in support of regulatory assessments of medicines, although recognizing the need to develop guidelines for best practices and to improve methods for collecting patient preferences.
Integration of patient-experience data in a new medicine application for an antidepressant treatment, in the context of FDA's Patient-Focused Drug Development Initiative (102)	To collect patient-experience data (using PROs and a patient preferences study using a discrete-choice survey) to inform the regulatory review.	The FDA considered that patient-experience data supported the antidepressant therapy. These findings highlight the value of integrating patient experience early in the medicines development process, right from early planning, especially for conditions such as depression, for which objective scales are lacking.

A patient preferences study conducted by Myeloma UK, in collaboration with the National Institute for Health and Care Excellence (NICE), with 475 patients with multiple myeloma (95)	To investigate how patient preference elicitation can be used in HTA, using DCEs. To assess the acceptability of trade-offs between benefits and risks for different treatment options from patients with multiple myeloma.	This study showed how preference elicitation can be collected from a large group of patients through an online survey. The study results helped to assess the acceptability of specific treatments and to identify which attributes are most important to patients when choosing between treatments. The study also reported considerable preference heterogeneity among patients.
Patient preferences for rheumatoid arthritis in a randomized control trial (93)	To identify the preferences of patients on an outcome measure for a randomized control trial, using DCEs.	This study provided an example of one approach to including patient preferences in the development of clinical trials. Researchers based the subsequent trial on the measure/instrument preferred by the patients.
A pilot study conducted by the German Institute for Quality and Efficiency in Health Care (IQWiG) on patient preferences for an	To examine whether DCEs can be used in health economic evaluations to identify, weigh, and prioritize patient-relevant outcomes.	The study findings suggest that it is possible to perform DCEs at the national level to support HTA.

antiviral therapy for hepatitis C (103)		
VALUE Study (Value and Utilities among European Patients) (104)	To assess the utility of the Measuring Attractiveness by a Categorical Based Evaluation Technique (MACBETH), a quantitative approach, for collecting preferences among multiple sclerosis patients.	A decision analytic tool like MACBETH can be easily included in the decision-making processes with a low cognitive burden for the majority of the patients.
Patient preference Information in Benefit-Risk Assessment, HTA, Pricing, and Reimbursement Decisions	A literature review was conducted to examine the use of patient preferences in decision-making.	Main objectives for assessing patient preferences: i) to prioritize outcome-specific information, ii) to value important treatment characteristics, iii) to provide patient-focused benefit–risk trade-offs, and iv) to appraise patients' willingness to pay for new technologies. Attributes assessed were predominantly efficacy and safety, and treatment convenience (*e.g.*, mode and frequency of administration). Attributes such as treatment cost, and HRQL were less frequently elicited.

4.3.3.1 Early Clinical Development

In the early steps of medicines development, assessing patient preferences can help to identify unmet medical needs, and to gain a better understanding of the disease, the personal experience and expectations of patients, and their acceptability of the benefit-risk profile. This information can inform resource allocation and guide the decision of which medical product should be primarily developed. Further, patient preferences information can help the design of novel therapeutics, tailoring its attributes to the most relevant outcomes for patients (9,14).

The industry should engage early with regulators and HTA bodies to discuss beforehand whether the novel medical product might benefit from patient preferences information and if so, how patient preferences can better support medicine development and regulatory assessment (14,104).

4.3.3.2 Clinical Trials

The use of patient preferences has the potential to inform clinical trial design, such as for the selection of patient-relevant clinical endpoints, and the definition of appropriate inclusion and exclusion criteria. Improving the selection of clinical endpoints relevant to patients will expectably lead to patients' increased willingness to participate in clinical trials and a potentially lower burden related to the elicitation, which means, improved recruitment, retention, and compliance of patients (9,14,85).

Although clinical trials can be a convenient opportunity to collect patient preferences data, consideration should be given to some limitations, namely: 1) participants might be prone to accept greater risk compared with other patients in real-world settings, 2) the results may not be generalizable to the rest of the patient population, 3) the results might differ depending on the timing of assessment (*e.g.*, patient *naïve* to the medicine at the beginning of the trial *vs* patient more familiar with the medicine at the end), or 4) the results may be subject to selection bias due to trial drop-out if patient preferences are elicited at a later time of a trial (9,14).

4.3.3.3 Regulatory Decision-Making

Historically, regulators have made regulatory decisions based on the evaluation of efficacy and safety data, multidisciplinary expertise, and clinical judgment. More recently patient input has been proposed as an added value to such decisions since it considers patients' values and unmet

needs, and not only clinical attributes but also social and ethical aspects that may influence trade-off decisions.

Patient preference methods can assess the relative weights between benefits and risks and what would be the maximum acceptable risk for a given health benefit, being particularly useful in more complex benefit-risk evaluations and assessments for early access. Moreover, patient preference elicitation may inform the patients' tolerance for uncertainty and whether they would use the medical product if it was approved. Finally, patient preference information may be included on the product label to inform the patients regarding benefits and risks (9,85,99). In the end, including patient preferences in marketing authorization applications might increase the understanding and acceptance of the decision, and the general trust in the decision-making process (85,92,105).

4.3.3.4 HTA and Reimbursement Decision-Making

Currently, HTA does not systematically include the perspective of patients and there are not enough published examples where preference evidence has been submitted as part of the reimbursement application to determine its impact. However, studies suggest that considering the patient perspective in HTA decisions could lead to more cost-effective outcomes and more efficient resource allocation (*i.e.*, reimbursement of only therapies that patients need and accept). Patient preferences could inform HTA on non-health attributes that are not captured by the traditional assessment tools, such as mode and frequency of administration. Furthermore, patient preferences input may also inform patients' preferred clinical outcomes, therefore supporting the weighting and selection of the most suitable endpoints for evaluation (8,9,14,85,91).

Several HTA bodies, such as NICE, the German HTA body IQWiG, and the Belgian HTA body "Belgian Health Care Knowledge Centre" (KCE), have shown a growing interest in using patient preferences for HTA, and have engaged in projects to advance this field (86). NICE does not acknowledge a role in the direct integration of patient preferences data in HTA evaluation models. Nonetheless, patient preferences evidence may be submitted in addition to clinical data to answer specific research questions. NICE argues that patient preferences input may be informative when two markedly different treatment options are being compared when there are multiple treatment options available to choose from, when treatment options have

important non-health benefits or when there is a significant patient preference heterogeneity. Hence, NICE has started to offer scientific advice for patient preference studies (86,95).

4.3.3.5 Post-Marketing

Throughout the post-marketing phase, patient preferences may inform patient acceptability of a given therapy in the real-world setting, extensions of indications, post-marketing surveillance, specific treatment opportunities, need for optimizing existing medical products, and product innovation (9,85,92). For instance, a preference study could be set up to understand patients' acceptance of post-approval rare but serious safety signals. Another example is the use of patient preferences when HTA bodies need to revise the status of reimbursement of a given treatment in the face of new treatment alternatives, since the new treatment landscape may determine different relevant endpoints and change the relative weight of treatment attributes. Finally, investigating revealed preferences in the post-marketing setting could add to the information provided by stated preferences and potentially improve external validity (1).

4.3.3.6 Clinical Practice Setting

It is well established that physicians should consider the individual preferences of patients in treatment decisions and hence patient preferences ought to be included in the context of clinical care, thus contributing to shared medical decision-making. Physicians should promote patient participation and empower patients to achieve informed preferences regarding, for example, treatment burden and treatment outcomes (95,97). Understanding patient preferences may also help to improve treatment recommendations and guidelines, ultimately shaping best clinical practices (93).

4.3.4 Initiatives and Guidance

Several efforts and initiatives have been undertaken to integrate patient preferences into the regulatory pathway. However, no consensus has yet been reached (8,9). The main initiatives and guidance recently developed are briefly presented hereafter.

4.3.4.1 European Medicines Agency

The EMA acknowledges the importance to include patient input in the regulatory process and recognizes the potential value of collecting patient preferences to aid in the regulatory process. The EMA's Regulatory Science to 2025 strategy has recommended including patient preferences to inform benefit-risk assessment and acknowledges the need to develop guidance based on recent studies and initiatives to inform the implementation, analysis, and identification of potential roles of preference studies, with the ultimate goal to enable a systematic and structured integration of patient preferences in the medical product life cycle (106).

EMA Benefit-Risk Methodology Project (107)

This project aimed to improve the consistency and transparency of the Agency benefit-risk assessment by reviewing methodological approaches that may aid regulatory decisions on the benefits and risks of medicines, including approaches to elicit patient preferences (92,107).

4.3.4.2 Other European Initiatives

Innovative Medicines Initiative – PREFER Project (108)

In 2015, the Innovative Medicines Initiative (IMI) launched the Patient Preferences in Benefit-Risk Assessments during the Drug Life Cycle project (Project PREFER), a public-private collaborative research project between the industry, academia, patient organizations, and an HTA organization. PREFER aimed to explore when and how patient preferences should be used to inform the decision-making process by regulatory and HTA bodies (108).

This 6-year project was divided into work packages. The methodology work package was responsible for investigating the concerns stakeholders may have about using patient-preference studies and provided recommendations on which methodologies should be used. The case study work package has conducted several studies based on the recommendations previously released. Table 8 summarizes the case studies conducted within the PREFER project. Finally, the recommendations work package launched a set of experience-based recommendations based on their work for patient preferences inclusion throughout the medical product life cycle. In turn, these recommendations will expectedly support the development of guidelines for industry, regulatory authorities, and HTA bodies. From this project arose several

publications, training materials, webinars to increase stakeholders' familiarity with patient preference studies, and operational guidance and other tools to aid in the design and execution of patient preference studies (108).

Table 8. PREFER project clinical patient preferences case studies. Adapted from Innovative Medicines Initiative (109).

Therapeutic area	**Clinical objectives**	**Medical product life cycle decision point of interest**
PREFER core case studies		
Neuromuscular diseases	- Elicit and quantify patient preferences including benefit to risk trade-offs (*e.g.* relative importance, minimum acceptable benefit, maximum acceptable risk) applicable for future neuromuscular disease treatments.	Pre-discovery
Rheumatoid arthritis	- Assess the preferences of people at risk of RA for preventive treatments. - Evaluate the maximum acceptable risk /Minimum acceptable benefit. - Characterize preference heterogeneity and characteristics that may explain heterogeneity.	Early development & post-marketing
Lung cancer	- Identify and quantify patient-relevant benefit-risk attributes of lung cancer treatments. - Quantify the risk tolerance for experiencing adverse events (Maximum Acceptable Risk) that patients are willing to accept for an increased probability of prolonged survival.	Post-marketing authorization

Additional case studies by public partners (academia)		
Diabetes	- Which attributes of blood glucose monitoring devices patients consider when deciding on their preferred device. - What is the relative importance of these different attributes in choosing which devices to use. - Assess the minimum acceptable benefits needed to justify increased costs.	Early development, HTA/reimbursement, post-marketing
Multiple Myeloma	- Identify patient-relevant benefit-risk attributes of multiple myeloma treatments (including upcoming treatments such as immunotherapy). - Quantify trade-offs for benefit-risk attributes of multiple myeloma treatments (including upcoming treatments such as immunotherapy).	Marketing authorisation, HTA/reimbursement
Hemophilia	- Identify attributes of gene therapy and standard of care that are important to patients. - Understand trade-offs that patients make when choosing between gene therapy and standard of care.	HTA/reimbursement
Rheumatoid Arthritis	- To elicit rheumatoid arthritis patients' preferences. - To estimate Minimum Acceptable Benefit. - To explain preference heterogeneity.	Marketing authorization & post-marketing
Lung Cancer, Neuromuscular diseases, Rheumatoid Arthritis	- Supplement the research findings of other core case studies in PREFER by assessing attribute attendance via eye-tracking.	Early development, pre-discovery, HTA/reimbursement, post-marketing

Additional case studies by private partners (industry)		
Chronic Obstructive Pulmonary Disease	- Quantify the relative needs and preferences of chronic obstructive pulmonary disease patients regarding symptoms, the impact on their quality of life, and evaluate whether preferences vary with certain respondent characteristics.	Input to phase III clinical trial design
Myocardial infarction	- To compare patient preferences for antithrombotic treatment attributes for patients with an acute MI and patients with chronic disease. - To assess preference heterogeneity in other relevant subgroups.	Post-marketing Pre-marketing: future developments
Chronic pain	- Quantify patient preferences for pharmaceutical treatments for chronic moderate-to-severe musculoskeletal pain associated with osteoarthritis and chronic low back pain. - Understand patients' preferences for, and potential trade-offs among, treatment attributes that are most relevant to them and that correspond to existing and future treatment options (*e.g.*,. nonsteroidal anti-inflammatory medicines, opioids, anti-NGF mAbs)	Pre-approval & late development

4.3.4.3 Food and Drug Administration

FDA: Patient Preference Information – Voluntary Submission, Review in PMAs, HDE Applications, and *de novo* Requests and Inclusion in Decision Summaries and Device Labelling: Final Guidance (88)

In the scope of the Patient Preference Initiative, the Center for Devices and Radiological Health (CDRH) issued guidance to encourage the submission of patient preferences information to support FDA's decision-making process. Although focused on medical devices, this guidance

covers some common aspects of patient preferences. It also provides recommendations for collecting and submitting preference studies and which attributes such studies should present. Moreover, the guidance outlines recommendations for the inclusion of patient preferences information in the product label. Finally, the guidance also presents hypothetical scenarios to illustrate how patient preferences may be used to inform FDA's decision-making (88).

A Framework for Incorporating Patient Preferences Regarding Benefits and Risks into Regulatory Assessment of Medical Technologies (89)

In 2015, the Medical Device Innovation Consortium (MDIC) issued a framework assessing patient preferences and their potential use and value in the regulatory context and beyond. This framework discusses in which situations patient preferences might be more valuable, what value patient preferences can offer in each stage of the MPLC, and when they should be collected. This report presents a catalogue of the available methods to assess patient preferences and outlines which factors to consider when conducting a patient preferences study and selecting a patient preference method. Finally, the MDIC framework identifies areas that require further work to advance the field of patient preferences and presents a glossary of terms related to patient preferences used throughout the document. Once more, although this framework concerns medical devices, it offers insights into other medical products (89).

4.3.5 Challenges and Limitations

Despite the potential of patient preferences in the decision-making throughout the MPLC and the initiatives undertaken, their current use has so far been limited. In fact, patient preferences information is currently not required for regulatory decision-making, being only considered as supplementary data. This is partly due to various methodological and pragmatic limitations identified in recent studies (4,8,85,87).

Stakeholders are still not familiar with patient preference methods and the role of patient preferences remains as yet unclear (85). The lack of specific guidance on how to incorporate patient preference studies in regulatory submissions is often pointed out as the major hurdle for advancing the implementation of patient preferences in the regulatory context. It is necessary to generate evidence supporting the implementation of patient preferences to motivate the industry and other stakeholders to engage in patient preference studies. On the other hand, to

support the development of such guidance, patient preference studies are needed to investigate best practices and issue recommendations based on those results.

The design and implementation of patient preference studies involve a significant investment of time and resources (*e.g.*, multidisciplinary expertise) (95). Nonetheless, some authors argue that the implementation of patient preferences will ultimately lead to cost reduction by making more efficient decisions (8,92). Nevertheless, according to Whitty *et al.*, while funding for patient preferences study may be more feasible during product development to support approval and/or reimbursement decisions, patient preferences information may be more valuable in earlier stages. (14)

Patient education is vital so that patients can properly contribute to the decision-making process and minimize the risk of information bias. The challenge is to provide sufficient information on the patients' role and the purpose of their input without being too burdensome. Doubts remain about the competency of patients to be involved in preference studies. Engaging with patient groups – which are overall better informed – may be an enticing solution to bypass this concern. However, attention should be given to the potential for creating selection bias (8,85).

Other concerns shared across various studies are related to the validity and reliability of patient preference studies, sample representativeness, the generalizability of results, and how to address preference heterogeneity. It remains unclear how and when patient preferences should be collected and used, who should conduct patient preferences studies to avoid potential bias, which patient preferences method should be used, how much weight patient preferences should receive, the impact that patient preferences can have on decision-making, and how the quality of patient preferences studies can be evaluated (4,8,85,87,104). It is also necessary to consider the consequences of potential bias that may occur since they can negatively and decidedly impact a regulatory decision (95).

4.4 A real case of the contribution of PROs and Patient Preferences: A Case Study of Multiple Myeloma

Multiple myeloma (MM) is a cancer of the bone marrow characterized by a proliferation of plasma cells in the bone marrow that most frequently affects elderly patients. The disruption of the normal functioning of the bone marrow results in several complications such as bone destruction, immunodeficiency with recurrent infections, impaired renal functioning, and anaemia (110–115). Thus, it is associated with substantial morbidity and mortality, with

patients reporting impaired physical functioning, pain, fatigue, physical and emotional burden. (114,115). The Global Cancer Observatory reported 176 404 new cases of MM worldwide in 2020, making this one of the most common hematologic malignancies (116,117). Importantly, due to the ageing of the population, the incidence of MM is expected to increase (118,119).

Despite several medicines being available, MM remains incurable. The course of MM progression is highly heterogeneous but usually involves periods of relapse and remission, as HRQL tends to progressively deteriorate throughout the course of the disease, *i.e.*, with each relapse (111,113,118,120,121). Still, advances in the treatment landscape have led to notable improvements in survival outcomes in MM patients. As result, a shift has been observed from an acute terminal disease to a chronic condition for many patients (122–125).

Although emerging therapeutic agents and treatment regimens are associated with extended survival, corresponding improvements in HRQL have been limited (126–128). With chronic treatment involving exposure to successive lines of therapy, patients face an increased risk of cumulative treatment-related toxicities that can have a significant impact on HRQL (117,123,129). This raises even greater concerns since older adults are more susceptible to adverse events due to their age inherent frailty, comorbidities, and polymedication (118,121). Thus, HRQL has become a key dimension of patient care and emerging therapies aim to preserve or improve HRQL while extending survival (117,120,130).

Considering the growing number and complexity of novel medicines and treatment regimens, and the high burden of both disease and treatments, there is a need to better understand the patients' perspectives on the impact of symptoms and treatments, their expectations, and preferences. In turn, their voices can be incorporated in the development of medicines to guide decision-making and improve HRQL beyond prolonging survival (114,117,121,123,131–133).

4.4.1 Patient-Reported Outcomes in Multiple Myeloma

It is acknowledged that MM is associated with a high symptom burden and worsening of HRQL (117,133). However, there are limited data on MM patient experience and the impact of available therapies (123,134). Furthermore, as the MM treatment landscape is rapidly evolving, it is vital to understand how these different treatment patterns affect outcomes beyond extending survival in order to improve MM management. For this reason, there has been an increasing focus on understanding patients' perspectives and how MM and respective treatments impact their HRQL using PROMs (123,129,133,135,136). In fact, major regulatory agencies such as

EMA and FDA have fully recognised the value of collecting PRO data in oncology studies to inform their decision-making (18,28).

Two recent reviews have provided an overview regarding the use of PROMs in MM trials. Efficace *et al.* identified 32 RCTs published between 2014 and 2021 for MM with a PRO endpoint, meaning a sharp increase in the number of RCTs including PROs over recent years. These results suggest that collecting and documenting PROs in medicines development is gaining increasing importance. In all studies, PROs were secondary or exploratory endpoints. More than half of all the RCTs published a secondary paper focused on PRO results. A previous review (135) aimed to provide details on the PROMs and PRO analysis used in MM registration trials between 2007 and 2020 from the FDA database. The authors identified 25 trials for MM, of which 17 (68%) included PRO data. In total, these trials evaluated 32 treatment regimens, either monotherapy or combination regimens. Similar to the review conducted by Efficace *et al.*, PROs were included as secondary or exploratory endpoints, in a proportion of 40% and 60%, respectively. Importantly, none of the PRO data collected on those trials were used to support labelling claims. Both studies identified that the most frequent PROM used in trials was the EORTC QLQ-C30 (a questionnaire developed to assess HRQL of cancer patients), either alone or with a MM disease-specific questionnaire, such as the MM disease-specific EORTC module named QLQ-MY20 (133,135).

While the added value of including PRO data in MM clinical trials has been proved, several caveats continue to limit its utility to inform decision-making (133). Both studies reported a lack of adherence to standard guidelines, meaning significant heterogeneity with respect to PRO study design (*e.g.*, PRO collection methods), statistical analysis, methods for handling missing data, and outcome reporting and interpretation. This is heightened by poor reporting and infrequent handling of missing data (133,135). Efficace *et al.* noticed suboptimal reporting for some items included on the CONSORT-PRO extension and the ISOQOL recommended standards for PRO reporting in scientific publications. For example, reasons for missing data were only explained in 9.4% of all trials, and the mode of administration of the PRO instrument was only described in 34.4% of all trials (133).

Such constraints make it difficult to compare results across studies and to derive robust conclusions. Thus, more consistency in the methodological approach to PRO assessment, interpretation, and reporting is needed (133,135). Nonetheless, as already pointed out, some key PRO methodological aspects have improved, as ongoing international efforts aim to standardize PRO methods (133).

Efficace and his colleagues also found varying criteria to define minimally important differences (MID), even in studies using the same PRO instruments, which further hampers PRO data interpretation and comparasion (133). As an example of a means to overcome this limitation, Sully and her colleagues (130) have generated estimates of the MID for each scale of the EORTC QLQ-MY20. Expectably, these standard MID will facilitate interpretation and comparison across MM study results (130).

Although data from clinical trials suggest that novel MM treatments present a favourable benefit/risk profile, available data is still limited and the extent to which these results are transferable to the real-world setting is still unclear (117). Some studies are now emerging in order to better understand how MM and respective treatments impact the HRQL of patients in the real-life context. Examples of such studies are presented hereafter.

An observational, cross-sectional, multicentre study (129) conducted in Germany in 2019 aimed to assess HRQL of 490 adults with MM by line of therapy. Results indicated that patients with MM had their HRQL negatively impacted, which also declined with increasing lines of therapy (129). Another observational, cross-sectional, multicentre study (117) conducted in France in 2016 was set to explore associations between treatment factors (*e.g.*, response, duration, and toxicity) and HRQL using PROMs. A longer duration of treatment was associated with higher HRQL scores. Moreover, patients receiving active treatment at later lines had better HRQL when compared to patients only receiving supportive care (117). Results from both studies emphasize the need for early and effective treatments to improve or maintain HRQL and delay disease progression (117,129). An observational, cross-sectional study (127) based in the United States had the goal to identify characteristics associated with poor HRQL from a sample of 690 patients. The survey results showed that worse socioeconomic status, higher comorbidities, not being in remission, and past receipt of radiation therapy were associated with poorer HRQL (127).

A few studies have also explored the use of PRO data to assess HRQL associated with given treatments. Leleu *et al.* (137) conducted an observational, prospective, multicentre study in six European countries between 2010 and 2014 with patients with relapsed/refractory MM (RRMM) beginning treatment with one of two different medicines for second- or third-line treatment. This study aimed to better understand how treatments for RRMM impact patients' HRQL in the real-life setting (137). More recently, another prospective cohort study also compared three treatment alternatives from a sample of patients with newly diagnosed MM (NDMM) from a US registry (138). A previous longitudinal study (139) used the same registry

to investigate HRQL of patients receiving maintenance therapy after autologous stem cell transplantation. Preliminary data suggested that maintenance therapy does not deteriorate HRQL while improving clinical outcomes (139).

As discussed earlier, PROM's can also assess adverse events. One observational, cross-sectional study (140) has focused on assessing the impact of Chemotherapy-Induced Peripheral Neuropathy (CIPN) – a side-effect of a specific medicine used for the treatment of MM – in HRQL using PROMs. This study has disclosed an unmet clinical need since CIPN was identified in a quarter of patients, is associated with psychological distress, and is still not effectively managed (140).

The voice of MM patients also has the potential to add value to HTA assessments. For example, Nikolaou *et al.* (141) performed a recent cost-utility analysis of a given medicine (comparing with a treatment alternative) for RRMM, from a commercial payer's perspective. HRQL was assessed by disease-specific PROMs (the EORTC QLQ-C30 and QLQ- MY20 questionnaires) and then converted into QALYs. The authors concluded that one of the treatment alternatives had lower costs, and increased QALYs, thus presenting added value (141).

PRO evidence (for example from clinical trials or real-world studies) should be considered in the clinical setting as it can help inform patients and manage their expectations during the course of the disease. For instance, newly diagnosed patients with MM can expect to improve their HRQL during first-line treatment. However, the same degree of improvement in HRQL is not expected to occur in patients with RRMM and they should be cognizant that their HRQL will presumably only stabilize. Additionally, PROs are important to monitor treatment effects and tolerability, and better understand the longitudinal impact of symptoms and treatments at different stages of the disease. In this context, PROs have the potential to inform clinicians' decisions for example to improve/adjust dose selection and to disclose specific patients' needs (*e.g.*, the need to address disease symptoms or adverse reactions) (122,133).

PROMs can also be employed to assess patient satisfaction. Comparing PRO scores from patients taking different treatments may disclose factors associated with treatment satisfaction. Through this approach, results from a recent (142) study suggested that shorter time spent receiving treatment and oral dosage forms were the strongest predictors of higher satisfaction with treatment convenience. In turn, increased treatment satisfaction is associated with improved adherence to the treatment and health outcomes (namely HRQL) (122,142).

Due to the importance of complementing clinical data with PROs, a recent study aimed at investigating the feasibility of routinely assessing ePROs to supplement a MM registry. Results from this study proved that routine ePRO monitoring is feasible from the perspective of both patients and clinicians, with no or little disturbance in clinical routine. The authors also described the implementation procedure, which can be useful for future similar initiatives.

As previously discussed in section 4.2.2., the development of a PRO instrument should begin with the construction of a conceptual framework to illustrate key concepts and their interrelationships. Therefore, Baz *et al.* (143) developed a conceptual framework to explore the concepts of MM and its treatment and their impact on patients' HRQL. Figure 5 presents the resulting conceptual framework as an example (143).

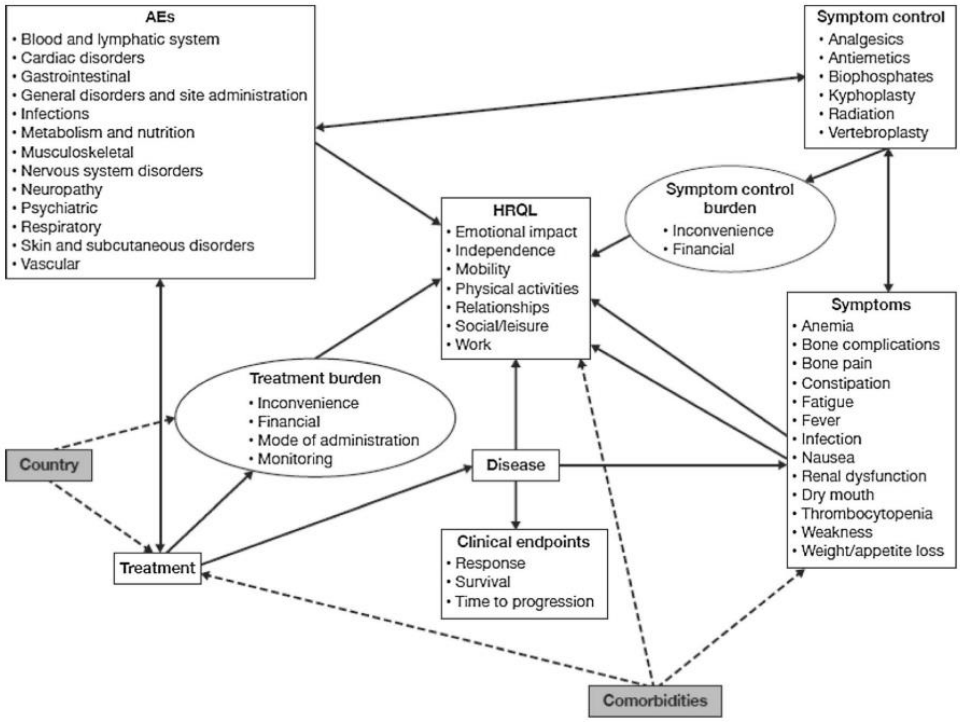

Figure 5. Example of a conceptual framework: Conceptual framework of factors affecting HRQL in MM. Retrieved from Baz *et al*. (143).

Current validated PRO instruments for MM were developed before the emergence of novel treatment options. Hence, these PROMs may lack the specificity required for this new treatment landscape. Therefore, a new PRO instrument was developed in 2021, called the multiple myeloma symptom and impact questionnaire (MySIm-Q) to enhance the measurement of MM outcomes. The study provides the rationale and methodology for developing the PRO instrument (113).

4.4.2 Patient Preferences in Multiple Myeloma

MM treatment landscape has seen remarkable progress, with several new therapies becoming available in recent years. However, these treatments differ in terms of mechanisms of action, clinical outcomes such as average length of survival, and safety profile, and other non-clinical aspects such as mode and frequency of administration, and treatment regimens (monotherapy or combination therapy, in some cases involving complex treatment regimens). Moreover, MM treatment is associated with uncertainties regarding long-term safety and efficacy (110,125,144).

Given the difficulties of MM management, patients with MM are faced with a complex trade--off between benefits and risks across treatment alternatives (125). Thus, the decisions involving treatments for MM are considered preference-sensitive. Retrieving the situations previously enounced in which a decision is regarded as preference-sensitive (see section 4.3.1.), the following ones apply to MM: 1) multiple treatment options are available but there is no option that is clearly superior for all patients, 2) the evidence favouring one option above others is uncertain or variable, 3) there is preference heterogeneity among patients and between patients and healthcare professionals (which will be further discussed), 4) there is a need to understand patients' acceptability for uncertainty regarding treatments such as long-term risks, and 5) treatment options have different risks comparing with the available treatment alternatives.

Notwithstanding the importance to understand patient preferences, current knowledge about this matter is limited (110,144). Nonetheless, this section provides real examples of how patient preference studies are being used to better understand the disease, identify unmet needs, inform regarding patients' tolerance for uncertainty, enhance shared decision-making, and to better understand preference heterogeneity. Current work is focusing on bringing real examples of the added value of patient preference studies, from medicines development and evaluation to clinical practice, and on outlining areas that may warrant further investigation.

Recent qualitative patient preference studies are helping to identify and explore key aspects of MM and its treatments that are most important to patients and therefore can impact patients' choices across treatment options. Studies from He *et al.* and Janssens *et al.* provide examples of exercises on these patient preference exploration methods (110,144).

He *et al.* aimed to investigate concepts of MM and its treatment that are most important to patients with NDMM and RRMM in the UK, France, and Germany. Additionally, the authors

intended to explore whether patients are willing to trade-off between benefits and risks for more convenient modes of administration. To this end, a literature review was conducted to develop a set of attributes regarding clinical benefits, HRQL, adverse events, and convenience. This literature review, along with a conceptual framework, informed the development of an interview guide. A two-part one-on-one telephone interview was carried out: the first half included open questions related to patients' experiences with MM to identify any new concepts, and the second half included semi-structured questions related to treatment experiences and questions related to benefit and risk of treatments from two different hypothetical treatment alternatives. According to the authors, results from this study were consistent with those from previous studies, *i.e.*, 1) participants prioritized increased life expectancy as the treatment benefit with the most value, 2) emphasized the need to improve quality of life and maintain the ability to carry out normal daily activities as a result of treatment, and 3) identified symptoms such as fatigue and bone pain, and adverse events such as gastrointestinal symptoms and peripheral neuropathy as considerably disruptive to HRQL. Furthermore, the study revealed new themes and concerns to add to the existing literature, including the burden of traveling for treatment and the overlap between adverse events and symptoms. These findings will inform a following quantitative study that is currently underway to elicit patients' benefit-risk trade-offs on key efficacy and safety outcomes of MM treatments (144).

Another study published in 2021 by Janssens *et al.* (110) also aimed to understand which disease and treatment-related characteristics, as well as types of attribute levels (*e.g.*, severity and duration), MM patients value the most for these to be included as attributes and levels in a future quantitative preference study. The study comprised of 1) an initial scoping review, which informed a 2) following focus group with MM patients across four European countries to reach a consensus on the most important characteristics, 3) and finally an analysis from a multi-stakeholder team with patients, patient organizations, clinicians, and preference research experts. The focus group aimed to understand which characteristics were of utmost importance to MM patients, understand the factors and dimensions influencing treatment attitudes and choices by patients with MM, and understand the language patients use to describe symptoms, treatment outcomes, and adverse events (so that those attributes and levels would be described in the same language). Participants placed significant expectations and hope that treatments would extend their life and lessen their signs and symptoms. However, they also raised important concerns with respect to uncertainties of the durability of positive treatment outcomes versus the severity, and duration of symptoms and side effects. These insights call for

transparent communication toward MM patients about treatment outcomes and uncertainties regarding their long-term efficacy and safety. Furthermore, this information may help medicine developers and regulators to understand which treatment outcomes and uncertainties are most relevant to people living with MM, and hence should be included in MM medicines' development and evaluation, and clinical practice (110).

As underlined by Janssens *et al.* (110), qualitative studies can help design a quantitative methodology. The authors stressed the importance of combining qualitative and quantitative methods since it may reduce the potential for misspecification of attributes and increase the validity of the results derived from quantitative research. In fact, all the MM quantitative preference studies identified in the present review followed an initial qualitative phase, usually using a focus-group discussion methodology, to inform the selection of the most suitable attributes and attribute levels. Subsequently, patient preference elicitation/quantitative methods can provide a quantified and structured understanding of individual patients' preferences, relative weights, and trade-offs (110). An overview of such quantitative studies is presented hereafter.

A recent quantitative study (111) examined the preferences for treatments in 94 patients with RRMM. DCE results revealed that patients placed the most weight on increasing progression-free survival and avoiding severe nerve damage. The authors also estimated that a third or more of the patients were cost-sensitive, *i.e.*, their treatment choice may depend on its cost. The study additionally included a BWS exercise which identified the risk of kidney failure, lowering white blood cell counts, and weakening of the immune system as the most bothersome treatment features (111).

A previous elicitation study (145) used two different quantitative methods, multicriteria decision analysis, and swing weighting, to elicit individual stated preferences from 560 patients with MM. Participants assigned the highest weight to progression-free survival, followed by severe or life-threatening toxicity, and mild or moderate chronic toxicity. The authors also conducted a decision analysis example to demonstrate the feasibility of using preference data to estimate patients' acceptance of specific MM treatments (145).

Wilke and his colleagues (146) also conducted a quantitative preference study to assess the preferences of 84 patients with RRMM regarding hypothetical novel combination treatments, using DCE. The survey results showed that the therapy application regimen was the most important attribute for patients with RRMM, followed by progression-free survival, the possibility of heart failure, and finally the possibility of adverse events affecting the blood.

Based on these results, the authors then estimated the treatment combinations with the highest overall utility. Moreover, according to the authors, these findings suggest that patients accept a lower progression-free time and/or higher adverse event rates in exchange for an all-oral therapy (146).

Most of the studies above presented identified preference heterogeneity (110,111,125,144,145). For instance, Auclair and his colleagues (111) have elicited preferences for treatments in patients with relapsed or refractory MM (RRMM) and identified two groups with different preferences: one preferring progression-free survival while the other favouring HRQL, *i.e.* minimization of toxicities. It remains to be understood this heterogeneity (111). A qualitative study conducted by He *et al.* (144) has explored preference heterogeneity between patients with newly diagnosed MM (NDMM) and relapsed or refractory MM (RRMM). The authors reported that although all patients reported the same symptoms, they were valued differently across patients with NDMM and RRMM. Concretely, the former group commonly stated bone pain and fatigue, while the latter often mentioned peripheral neuropathy and infections. The authors have hypothesized that this discrepancy may be related to the safety profiles of different MM regimens used in NDMM and RRMM (144). Another qualitative study conducted by Janssens *et al*. found preference heterogeneity across subgroups of patients with MM. For example, patients more often valued those symptoms and adverse events they had previously experienced. Additionally, the results also suggested that patients who were older, had undergone more treatments, or had no children placed more value on quality of life than life expectancy, and vice versa (110). Similarly, in a quantitative survey led by Postmus *et al.* (145), participants who ranked severe or life-threatening toxicity above mild or moderate chronic toxicity were more commonly younger, working, and caring for dependent family members and had more frequently experienced severe or life-threatening adverse events (145). Lastly, Fifer *et al.* (125) investigated the treatment preferences of patients with MM compared to physicians, nurses, as well as caregivers. This quantitative study revealed considerable heterogeneity in preferences for treatment attributes, especially regarding the magnitude of importance placed on overall survival, remission period, and out-of-pocket costs. For example, physicians and nurses tended to be more concerned with overall survival and more cost-sensitive than patients with MM (125). The preliminary data from these studies will inform areas of unmet needs and future research, which in turn has the potential to guide the development of medicines that are tailored to patients' needs, and to impact decision-making regarding the value of new

medicines, and treatment choices. In the long run, it will improve HRQL and other significant clinical outcomes for people living with MM (110,125,144).

Finally, at the individual level, PROs can improve clinical decision-making. As previously stated, decisions involving treatments for MM are considered preference-sensitive, and there is a significant preference heterogeneity between patients and healthcare providers, which means that medical decisions surrounding MM may often not reflect patients' preferences and needs. Considering patients' preferences as part of shared decision-making is therefore paramount. To achieve this, it is necessary to foster transparent communication in order to enable patient empowerment in treatment decisions. Those practices will expectedly increase treatment satisfaction regarding treatment decisions and altogether manage patients' expectations, increase adherence to treatment, and ultimately result in better outcomes and quality of life for people living with MM (110,125).

A further study worth mentioning is that of Lassalle *et al.* (147) who assessed patient preference with regards to home *versus* hospital administration of a subcutaneous medicine. Afterwards, a cost analysis was performed to compare the average cost of an injection of the medicine at the hospital and at home. The cost analysis showed that home administration resulted in a reduction of cost of 20% compared with hospital administration. Furthermore, there was a clear preference for home administration from the patients with MM, leading to improvement in their HRQL. This study illustrates how patient preferences may complement economic evaluations and guide payers' decision-making (147).

In essence, there is a need for valid, meaningful, and comprehensive patient preference research on MM treatments since very little literature has been published to this date (110,111,125,144). Therefore, the work recently made will lay the foundation for future research and guidance on this matter.

One of the drawbacks underscored in some of the aforementioned studies is related to the significant heterogeneity of methodologies used between studies, hampering the ability to compare results across such studies (110,146). As pointed out by Janssens and her colleagues, these studies provide experience-based learnings on the design, conduct, and analysis of preference studies, and hopefully, these methodological learnings may lead to the development of a standardized and validated approach that can enable comparison between patient preference studies (110).

4.5 Patient Reported Outcomes and Patient Preferences: Differences and Commonalities in a glimpse

PRO instruments intend to measure a patient's perception of a health status or a change in health status in a given moment, reported by himself/herself. They capture disease burden and/or treatment effect over time. Patient preferences focus on assessing what matters most to patients, providing information regarding trade-offs between treatment attributes (87,88,92,95). In the words of Mera *et al.*, "*PROs help assess where the patient is at a particular time point, but do not indicate where the patient wants to go*" (97). Table 9 outlines some of the key differences between PROs and patient preferences.

Table 9. Differences between patient preferences and patient reported outcomes. Adapted from Myeloma UK & National Institute for Health and Care Excellence (95).

Type of measure	Patients-reported outcomes	Patient preferences
Objective	Measuring the health status of the patient.	Valuing health states, outcomes, or attributes of treatments.
Temporal focus	Real-time, before/after an intervention.	Preferences are relatively enduring, though may change over time.
Domains	Pre-defined domains (*e.g.*, mobility, self-care, usual activities, pain/discomfort, or symptoms).	Outcomes/attributes selected according to study objectives.

Although PROMs can assess treatment experiences, they usually focus on the disease and its impact as reported by the patient. Inversely, while patient preferences may focus on disease experience, they are usually used to collect data on the choices patients make when faced with different treatment alternatives. Moreover, while stated preferences can assess how patients believe they would react to hypothetical treatments, PROs cannot provide data regarding treatments that patients have not experienced yet (148,149).

PRO research and patient preference research have traditionally been conducted separately and used mainly for distinct ends. Patient preferences have been more explored by

health/behavioural economists, epidemiologists, and market researchers for HTA purposes, and to support commercialization strategies. On the other hand, PROs have been essentially used in the context of medicines' development and evaluation. Likewise, PRO data are more frequently obtained from trial populations during medicines' development whilst patient preference data is often obtained from observational cohorts (who may not have experienced the treatment of interest in the case of stated preferences) (149). In that sense, PRO and patient preference data are not usually gathered from the same patients. Nevertheless, as argued by Reaney *et al.* (149), some situations might benefit from the assessment of both PROs and patient preferences data from the same patients, for example:

- When a PRO assessment reveals an improvement in some symptoms and worsening of others, patient preference elicitation may be useful to understand whether patients value most the improved or the worsened symptoms.
- If there is a clinical improvement accompanied by treatment-related toxicity reported by PROMs, patient preference elicitation methods can be used to understand the extent to which patients might be willing to accept the risk in exchange for the clinical benefit.

Figure 6 presents the main domains of patient experience data and with what method(s) (PROs and/or patient preferences) they are usually captured.

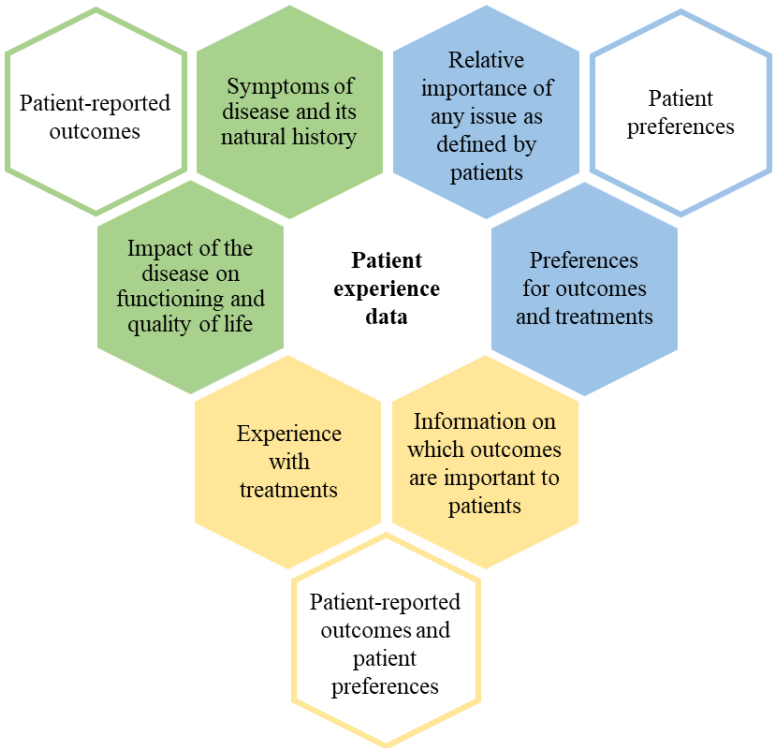

Figure 6. Methodologies used to assess different domains of patient experience data. (149)

In fact, since patient experience information comprises data from both PROs and patient preferences, there is an opportunity for combining the use of PRO and patient preference methodologies in favour of generating more robust and complementary data regarding patients' experiences, perspectives, needs, and priorities. Additionally, PRO and patient preference research can mutually inform each other. For instance, if the items of validated PRO instruments are in line with the attributes identified in a qualitative patient preference study, there is a mutual validation of those items and attributes in the sense that they are indeed important to patients. In a different scenario, results from a qualitative patient preference study could inform additional issues of importance to patients not represented in available PRO instruments. Thus, patient preference data has the potential to inform the development and enhancement/update of PROMs. In turn, PRO concepts can also inform the design of a patient preference study (148,149).

Although there are key differences, PROs and patient preferences also share some similarities worth mentioning: 1) both methodologies aim at collecting patient experience data to inform decision-making, 2) both apply mixed-methods approaches (*e.g.*, exploratory qualitative research for concept/attribute elicitation to support the development of quantitative studies), 3) and both methods can be employed within a clinical trial or observational study, in parallel to a clinical trial or observational study, and during routine clinical practice (149).

The case study conducted in MM reinforces what was found in literature nonspecific to this disease: in terms of representativity, few examples of patient preference research are published when compared with PROs. This translates into poorer incorporation of patient preference information in decision-making. For example, while PROs are more frequently being used as endpoints in clinical trials, patient preferences' utility in the R&D and regulatory contexts is still limited.

Still regarding MM, studies published on this matter provided some practical examples of the potential roles of PROs and patient preferences research. As previously detailed and similarly to other clinical areas, while most PRO studies focus on assessing outcomes related to the impact of the MM and its treatments, such as symptoms and HRQL, patient preferences research aims at investigating which disease- and treatment-related characteristics are of utmost importance to patients, exploring patients' trade-offs across attributes, understanding patients' acceptability for uncertainty regarding MM treatments, and identifying and characterizing preference heterogeneity. In doing so, these methodologies have proved to offer complementary

information about MM patients' experiences and have the potential to tailor medicines development and clinical care to patients' needs, priorities, and values.

5 Conclusions

There has been a growing recognition of the value of including patients' experiences and perspectives in decision-making throughout the MPLC. This increased focus towards patient--centricity and shared decision-making has created the need to develop methods capable of gathering patient input in a robust, systematic, and meaningful way. To this end, PROs and patient preferences research have been pointed out as suitable methods for collecting patient experience data to inform decision-making.

The present thesis provided an overview of PROs and patient preferences input over recent years by documenting their potential roles throughout the medicines' life cycle, main methodological aspects, challenges and limitations, ongoing efforts and initiatives to advance research and implementation, and key recommendations for future research, as reported by the current literature.

Since the lack of a global framework is hampering the effective incorporation of patient input in decision-making, the literature is unanimous regarding the need for clear and harmonized guidance for the routine use of PROs and patient preferences. Notwithstanding these limitations, there has been considerable progress provided by public-private partnerships and efforts led by major regulatory agencies such as EMA and FDA. There is a call to action and continuous efforts and international multistakeholder collaboration are needed to consolidate learnings from ongoing research and foster consistent best practices that guide the implementation of patient engagement.

While evidence on patient involvement is still being built and a long road is still ahead, numerous opportunities for using PROs and patient preferences have been identified, from early medicines development to post-marketing and routine clinical decisions. It is expected that systematic and effective collection, analyses, and sharing of patient experience data will maximise its utility and ultimately benefit patients and the healthcare ecosystem.

References

1. Innovative Medicines Initiative. PREFER Recomendations: Why, when and how to assess and use patient preferences in medical product decision-making [Internet]. 2022 [cited 2022 Apr 20]. Available from: https://www.imi-prefer.eu/recommendations/

2. U.S. Food and Drug Administration. Collecting Patient Experience Data: How You Can Best Help Fda? [Internet]. 2017 [cited 2022 Jun 18]. Available from: https://www.fda.gov/media/112163/download?fbclid=IwAR2d-Rxm6N6zKj2FvEwTRbYQ7qGrVKvxFLElhFBrk3t99jkY3hQzu6yyoRo

3. Zhou Z, Hultgren KE. Complementing the US Food and Drug Administration adverse event reporting system with adverse drug reaction reporting from social media: Comparative analysis. JMIR Public Heal Surveill. 2020;6(3):1–12.

4. van Overbeeke E, Forrester V, Simoens S, Huys I. Use of Patient Preferences in Health Technology Assessment: Perspectives of Canadian, Belgian and German HTA Representatives. Patient [Internet]. 2021;14(1):119–28. Available from: https://doi.org/10.1007/s40271-020-00449-0

5. U.S. Food and Drug Administration. Patient-Focused Drug Development: Collecting Comprehensive and Representative Input Guidance for Industry, Food and Drug Administration Staff, and Other Stakeholders [Internet]. Draft Guidance. 2020 [cited 2022 Feb 14]. Available from: https://www.fda.gov/drugs/guidance-compliance-regulatory-information/guidances-drugsand/or

6. Simon TA, Khouri MS, Kou TD, Gomez-Caminero A. Realizing the Potential of the Patient Perspective. Patient Prefer Adherence [Internet]. 2020 Oct;Volume 14:2001–7. Available from: https://www.dovepress.com/realizing-the-potential-of-the-patient-perspective-peer-reviewed-article-PPA

7. Hansen MB, Nørgaard LS, Hallgreen CE. How and Why to Involve Patients in Drug Development: Perspectives From the Pharmaceutical Industry, Regulatory Authorities, and Patient Organizations. Ther Innov Regul Sci [Internet]. 2019 Aug 7; Available from: http://journals.sagepub.com/doi/10.1177/2168479019864294

8. Chachoua L, Dabbous M, François C, Dussart C, Aballéa S, Toumi M. Use of Patient Preference Information in Benefit–Risk Assessment, Health Technology Assessment, and Pricing and Reimbursement Decisions: A Systematic Literature Review of Attempts

and Initiatives. Front Med. 2020;7(October):1–14.

9. van Overbeeke E, Whichello C, Janssens R, Veldwijk J, Cleemput I, Simoens S, et al. Factors and situations influencing the value of patient preference studies along the medical product lifecycle: a literature review. Drug Discov Today [Internet]. 2019;24(1):57–68. Available from: https://doi.org/10.1016/j.drudis.2018.09.015

10. Hoos A, Anderson J, Boutin M, Dewulf L, Geissler J, Johnston G, et al. Partnering With Patients in the Development and Lifecycle of Medicines: A Call for Action. Ther Innov Regul Sci [Internet]. 2015 [cited 2022 Jun 19];49(6):929–39. Available from: http://mrct.globalhealth.harvard.edu/

11. Lowe MM, Blaser DA, Cone L, Arcona S, Ko J, Sasane R, et al. Increasing Patient Involvement in Drug Development. Value Heal [Internet]. 2016;19(6):869–78. Available from: http://dx.doi.org/10.1016/j.jval.2016.04.009

12. U.S. Food and Drug Administration. FDA and European Medicines Agency Patient Engagement Cluster [Internet]. [cited 2022 Jun 14]. Available from: https://www.fda.gov/patients/learn-about-fda-patient-engagement/fda-and-european-medicines-agency-patient-engagement-cluster

13. European Medicines Agency. Terms of reference for the EMA/ FDA cluster on patient engagement [Internet]. 2016 [cited 2022 Jun 14]. Available from: https://www.ema.europa.eu/en/documents/other/terms-reference-european-medicines-agency/food-drug-administration-cluster-patient-engagement_en.pdf

14. Whitty JA, de Bekker-Grob EW, Cook NS, Terris-Prestholt F, Drummond M, Falchetto R, et al. Patient Preferences in the Medical Product Lifecycle. Patient - Patient-Centered Outcomes Res [Internet]. 2020 Feb 29;13(1):7–10. Available from: https://doi.org/10.1007/s40271-019-00400-y

15. Reaney M, Cline J, Wilson JC, Posey M. Generating Relevant Information from Patients in the Technology-Enhanced Era of Patient-Focused Drug Development: Opportunities and Challenges. Patient [Internet]. 2021;14(1):11–6. Available from: https://doi.org/10.1007/s40271-020-00455-2

16. U.S. Food and Drug Administration. Patient-Focused Drug Development: Industry, Food and Drug Administration. Methods to Identify What Is Important to Patients Guidance for Staff, and Other Stakeholders [Internet]. 2019. Available from:

http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htmand/or

17. Bourke A, Dixon WG, Roddam A, Lin KJ, Hall GC, Curtis JR, et al. Incorporating patient generated health data into pharmacoepidemiological research. Pharmacoepidemiol Drug Saf. 2020;(October):1540–9.

18. European Medicines Agency. Appendix 2. Guideline on the evaluation of anticancer medicinal products in man: The use of patient-reported outcome (PRO) measures in oncology studies [Internet]. 2016 [cited 2022 Feb 5]. Available from: www.ema.europa.eu/contact

19. Joseph C, Kelly Z, Andrew B, Jose A, Demissie A, Tara S. Patient-Reported Outcomes Measurement, Implementation and Interpretation. Chapman and Hall/CRC, editor. New York; 2016.

20. European Medicines Agency. Reflection Paper on the use of patient reported outcome (PRO) measures in oncology studies. 2014.

21. Mckown S, Acquadro C, Anfray C, Arnold B, Eremenco S, Giroudet C, et al. Good practices for the translation, cultural adaptation, and linguistic validation of clinician-reported outcome, observer-reported outcome, and performance outcome measures. J Patient-Reported Outcomes [Internet]. 2020; Available from: https://doi.org/10.1186/s41687-020-00248-z

22. Storf M. The impact of FDA and EMA guidances regarding Patient Reported Outcomes (PRO) on the drug development and approval process Wissenschaftliche Prüfungsarbeit. 2013; Available from: http://dgra.de/deutsch/studiengang/master-thesis/2013-Max-Storf-The-impact-of-FDA-and-EMA-guidances-regarding-Patient-Reported-O

23. Cella D, Hahn E, Jensen S, Butt Z, Nowinski C, Rothrock N, et al. Patient-Reported Outcomes In Performance Measurement. RTI Press Book series. USA: Research Triangle Institute; 2015.

24. Williams K, Sansoni J, Morris D, Grootemaat P, Thompson C. Patient-reported outcome measures: Literature Review. Pharmacoeconomics: From Theory to Practice. 2016. 149–162 p.

25. Snyder C, Wu AW, editors. Users' Guide to Integrating Patient-Reported Outcomes in Electronic Health Records [Internet]. Baltimore, MD: Johns Hopkins University; 2017

[cited 2022 Feb 15]. Available from: http://www.pcori.org/document/users-guide-integrating-patient-reported-outcomes-

26. Nixon A, Muehlhausen W, Wild D. Patient Reported Outcomes: An overview. Torino: SEEd; 2015.

27. Giesinger JM, Efficace F, Aaronson N, Calvert M, Kyte D, Cottone F, et al. Past and Current Practice of Patient-Reported Outcome Measurement in Randomized Cancer Clinical Trials: A Systematic Review. Value Heal. 2021;24(4):585–91.

28. U.S. Food and Drug Administration. Core Patient-Reported Outcomes in Cancer Clinical Trials Guidance for Industry (Draft Guidance) [Internet]. 2021. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/core-patient-reported-outcomes-cancer-clinical-trials

29. Kluetz PG, O'Connor DJ, Soltys K. Incorporating the patient experience into regulatory decision making in the USA, Europe, and Canada. Lancet Oncol [Internet]. 2018;19(5):e267–74. Available from: http://dx.doi.org/10.1016/S1470-2045(18)30097-4

30. NIH Collaboratory Coordinating Center. Rethinking Clinical Trials: Patient-Reported Outcomes [Internet]. 2014. Available from: https://rethinkingclinicaltrials.org/cores-and-working-groups/patient-reported-outcomes-2/

31. Aaronson N, Choucair A, Elliott T. User's guide to implementing patient-reported outcomes assessment in clinical practice. Int Soc Qual Life Res [Internet]. 2011;(January):57. Available from: http://www.isoqol.org/UserFiles/file/UsersGuide.pdf

32. Bansal D, Bhagat A, Schifano F, Gudala K. Role of patient-reported outcomes and other efficacy endpoints in the drug approval process in Europe (2008-2012). J Epidemiol Glob Health [Internet]. 2015 [cited 2022 Feb 15];5(4):385–95. Available from: https://doi.org/10.1016/j.jegh.2015.04.006

33. Haag S, Junge L, Lotz F, McGauran N, Paulides M, Potthast R, et al. Results on patient-reported outcomes are underreported in summaries of product characteristics for new drugs. J Patient-Reported Outcomes [Internet]. 2021;5(1):1–7. Available from: https://doi.org/10.1186/s41687-021-00402-1

34. Jarosławski S, Auquier P, Borissov B, Dussart C, Toumi M. Patient-reported outcome

claims in European and United States orphan drug approvals. J Mark Access Heal Policy [Internet]. 2018;6(1):1542920. Available from: https://doi.org/10.1080/20016689.2018.1542920

35. Gnanasakthy A, Barrett A, Evans E, D'Alessio D, Romano C (DeMuro). A Review of Patient-Reported Outcomes Labeling for Oncology Drugs Approved by the FDA and the EMA (2012-2016). Value Heal [Internet]. 2019 Feb [cited 2021 Nov 6];22(2):203–9. Available from: https://doi.org/10.1016/j.jval.2018.09.2842

36. Marandino L, La Salvia A, Sonetto C, De Luca E, Pignataro D, Zichi C, et al. Deficiencies in health-related quality-of-life assessment and reporting: A systematic review of oncology randomized phase III trials published between 2012 and 2016. Ann Oncol [Internet]. 2018 Dec 1 [cited 2022 Feb 15];29(12):2288–95. Available from: https://pubmed.ncbi.nlm.nih.gov/30304498/

37. Hamel JF, Saulnier P, Pe M, Zikos E, Musoro J, Coens C, et al. A systematic review of the quality of statistical methods employed for analysing quality of life data in cancer randomised controlled trials. Vol. 83, European Journal of Cancer. Pergamon; 2017. p. 166–76.

38. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. ICH Reflection paper Proposed: Proposed ICH Guideline Work to Advance Patient Focused Drug Development. Vol. 4. 2021.

39. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. Outcome of public consultation on ICH Reflection Paper on Patient-Focused Drug Development (PFDD). 2021.

40. European Medicines Agency. Reflection Paper on the Regulatory Guidance for the Use of Health- Related Quality of Life (HRQL) Measures in the Evaluation of Medicinal Products. 2005.

41. Calvert M, Kyte D, Mercieca-Bebber R, Slade A, Chan AW, King MT. Guidelines for inclusion of patient-reported outcomes in clinical trial protocols the spirit-pro extension. JAMA - J Am Med Assoc [Internet]. 2018 Feb 6 [cited 2022 Feb 15];319(5):483–94. Available from: https://jamanetwork.com/journals/jama/fullarticle/2671472

42. Reeve BB, Wyrwich KW, Wu AW, Velikova G, Terwee CB, Snyder CF, et al. ISOQOL recommends minimum standards for patient-reported outcome measures used in patient-

centered outcomes and comparative effectiveness research. Qual Life Res [Internet]. 2013 Oct [cited 2022 Feb 15];22(8):1889–905. Available from: https://pubmed.ncbi.nlm.nih.gov/23288613/

43. Coens C, Pe M, Dueck AC, Sloan J, Basch E, Calvert M, et al. International standards for the analysis of quality-of-life and patient-reported outcome endpoints in cancer randomised controlled trials: recommendations of the SISAQOL Consortium. Lancet Oncol [Internet]. 2020 Feb;21(2):e83–96. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1470204519307909

44. Patrick D. Reporting of patient-reported outcomes in randomized trials: The CONSORT PRO extension [Internet]. Vol. 16, Value in Health. 2013 [cited 2022 Feb 15]. p. 455–6. Available from: http://dx.doi.org/10.1016/j.jval.2013.04.001

45. The PROTEUS-Trials Consortium (Patient-Reported Outcome Tools: Engaging Users and Stakeholders). PROTEUS Handbook. Prepared by The University of Sydney Quality of Life Office for the PROTEUS-Trials Consortium. [cited 2022 Feb 15]; Available from: www.TheProteusConsortium.org

46. Calvert M, King M, Mercieca-Bebber R, Aiyegbusi O, Kyte D, Slade A, et al. SPIRIT-PRO Extension explanation and elaboration: guidelines for inclusion of patient-reported outcomes in protocols of clinical trials. BMJ Open. 2021;11(6).

47. Brundage M, Blazeby J, Revicki D, Bass B, De Vet H, Duffy H, et al. Patient-reported outcomes in randomized clinical trials: Development of ISOQOL reporting standards. Qual Life Res [Internet]. 2013 Aug [cited 2022 Feb 15];22(6):1161–75. Available from: https://pubmed.ncbi.nlm.nih.gov/22987144/

48. Engel P, Almas MF, De Bruin ML, Starzyk K, Blackburn S, Dreyer NA. Lessons learned on the design and the conduct of Post-Authorization Safety Studies: review of 3 years of PRAC oversight. Br J Clin Pharmacol [Internet]. 2017 Apr 7 [cited 2022 Feb 11];83(4):884–93. Available from: https://onlinelibrary.wiley.com/doi/10.1111/bcp.13165

49. Low CA. Harnessing consumer smartphone and wearable sensors for clinical cancer research. npj Digit Med [Internet]. 2020 Dec 27;3(1):140. Available from: https://www.nature.com/articles/s41746-020-00351-x

50. Gensheimer SG, Wu AW, Snyder CF, Basch E, Gerson J, Holve E, et al. Oh, the Places

We'll Go: Patient-Reported Outcomes and Electronic Health Records. Patient [Internet]. 2018 Dec 1 [cited 2022 Feb 16];11(6):591–8. Available from: https://pubmed.ncbi.nlm.nih.gov/29968179/

51. Horn ME, Reinke EK, Mather RC, O'Donnell JD, George SZ. Electronic health record–integrated approach for collection of patient-reported outcome measures: a retrospective evaluation. BMC Health Serv Res [Internet]. 2021 [cited 2022 Feb 16];21(1). Available from: https://doi.org/10.1186/s12913-021-06626-7

52. Franklin PD, Chenok KE, Lavalee D, Love R, Paxton L, Segal C, et al. Framework To Guide The Collection And Use Of Patient-Reported Outcome Measures In The Learning Healthcare System. eGEMs (Generating Evid Methods to Improv patient outcomes). 2017;5(1):17.

53. O'Rourke B, Oortwijn W, Schuller T. The new definition of health technology assessment: A milestone in international collaboration [Internet]. Vol. 36, International Journal of Technology Assessment in Health Care. 2020 [cited 2022 Feb 12]. p. 187–90. Available from: https://doi.org/10.1017/S0266462320000215

54. Inotai A, Jakab I, Brixner D, Campbell JD, Hawkins N, Kristensen LE, et al. Proposal for capturing patient experience through extended value frameworks of health technologies. Vol. 27, Journal of Managed Care and Specialty Pharmacy. 2021. p. 936–47.

55. Pratt-Chapman M, Bhadelia A. Patient-reported outcomes in health economic decision-making: A changing landscape in oncology [Internet]. Vol. 213, Recent Results in Cancer Research. Springer International Publishing; 2019. 67–83 p. Available from: http://dx.doi.org/10.1007/978-3-030-01207-6_6

56. Brogan AP, DeMuro C, Barrett AM, D'Alessio D, Bal V, Hogue SL. Payer perspectives on patient-reported outcomes in health care decision making: Oncology examples. J Manag Care Spec Pharm [Internet]. 2017 [cited 2022 Feb 11];23(2):125–34. Available from: www.jmcp.org

57. Calvert M, Kyte D, Price G, Valderas JM, Hjollund NH. Maximising the impact of patient reported outcome assessment for patients and society. BMJ [Internet]. 2019 [cited 2022 Feb 11];364. Available from: http://www.bmj.com/

58. Weldring T, Smith SMS. Article Commentary: Patient-Reported Outcomes (PROs) and

Patient-Reported Outcome Measures (PROMs). Vol. 6, Health Services Insights. SAGE Publications Ltd; 2013.

59. U.S. Food and Drug Administration. Guidance for Industry Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims. 2009.

60. Eton DT, Shevrin DH, Beaumont J, Victorson D, Cella D. Constructing a conceptual framework of patient-reported outcomes for metastatic hormone-refractory prostate cancer. Value Heal [Internet]. 2010;13(5):613–23. Available from: http://dx.doi.org/10.1111/j.1524-4733.2010.00702.x

61. Frei A, Puhan M. Assessment of Patient-Reported Outcomes. In: Clini E, Holland A, Pitta F, Troosters T, editors. Textbook of Pulmonary Rehabilitation [Internet]. Cham: Springer International Publishing; 2018. p. 93–107. Available from: http://link.springer.com/10.1007/978-3-319-65888-9_7

62. Rothman ML, Beltran P, Cappelleri JC, Lipscomb J, Teschendorf B, Sloan JA. Patient-reported outcomes: Conceptual issues. Value Heal [Internet]. 2007;10(SUPPL. 2):S66–75. Available from: http://dx.doi.org/10.1111/j.1524-4733.2007.00269.x

63. Willke RJ. Measuring the value of treatment to patients: patient-reported outcomes in drug development. Am Heal drug benefits [Internet]. 2008;1(1):34–40. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25126209%0Ahttp://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC4114029

64. National Institutes of Health. Endpoint - Toolkit for Patient-Focused Therapy Development [Internet]. [cited 2022 Feb 13]. Available from: https://toolkit.ncats.nih.gov/glossary/endpoint/

65. Harvard Clinical and Translational Science Center. Outcome Measure Considerations for Clinical Trials Reporting on ClinicalTrials.gov. Harvard Catal [Internet]. 2018 [cited 2022 Feb 13];1–5. Available from: https://catalyst.harvard.edu/wp-content/uploads/regulatory/CTR3_OutcomeMeasures.pdf

66. Terwee CB, Bot SDM, De Boer MR, Van Der Windt DAWM, Knol DL, Dekker J, et al. Quality criteria were proposed for measurement properties of health status questionnaires.

67. U.S. Food and Drug Administration. Patient-Focused Drug Development Guidance Public Workshop: Methods to identify what is important to patients & select, develop or

modify fit-for-purpose clinical outcomes assessments. Discussion Document [Internet]. Patient-Focused Drug Development Guidance. 2018 [cited 2021 Nov 20]. Available from: https://www.fda.gov/downloads/Drugs/NewsEvents/UCM620708.pdf

68. Warsame R, D'Souza A. Patient Reported Outcomes Have Arrived: A Practical Overview for Clinicians in Using Patient Reported Outcomes in Oncology. Mayo Clin Proc [Internet]. 2019 Nov;94(11):2291–301. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0025619619303556

69. Bottomley A, Pe M, Sloan J, Basch E, Bonnetain F, Calvert M, et al. Analysing data from patient-reported outcome and quality of life endpoints for cancer clinical trials: a start in setting international standards. Lancet Oncol. 2016;17(11):e510–4.

70. Lombardi P, Marandino L, De Luca E, Zichi C, Reale ML, Pignataro D, et al. Quality of life assessment and reporting in colorectal cancer: A systematic review of phase III trials published between 2012 and 2018. Crit Rev Oncol Hematol [Internet]. 2020;146:102877. Available from: https://doi.org/10.1016/j.critrevonc.2020.102877

71. Calvert MJ, O'Connor DJ, Basch EM. Harnessing the patient voice in real-world evidence: the essential role of patient-reported outcomes. Nat Rev Drug Discov. 2019;18(10):731–2.

72. Wong RL, Morgans AK. Integration of Patient Reported Outcomes in Drug Development in Genitourinary Cancers. Curr Oncol Rep. 2020;22(3):9–11.

73. Cruz Rivera S, McMullan C, Jones L, Kyte D, Slade A, Calvert M. The impact of patient-reported outcome data from clinical trials: perspectives from international stakeholders. J Patient-Reported Outcomes [Internet]. 2020 [cited 2022 Feb 15];4(1). Available from: https://doi.org/10.1186/s41687-020-00219-4

74. Kalluri M, Luppi F, Vancheri A, Vancheri C, Balestro E, Varone F, et al. Patient-reported outcomes and patient-reported outcome measures in interstitial lung disease: Where to go from here? Eur Respir Rev. 2021;30(160).

75. National Quality Forum. Patient Reported Outcomes (PROs) in Performance Measurement. 2013;1–35.

76. McGee RG. How to Include Patient-Reported Outcome Measures in Clinical Trials [Internet]. Vol. 18, Current Osteoporosis Reports. Springer; 2020 [cited 2022 Feb 15]. p. 480–5. Available from: https://link.springer.com/article/10.1007/s11914-020-00611-

5

77. Tykodi SS, Schadendorf D, Cella D, Reck M, Harrington K, Wagner S, et al. Patient-reported outcomes with nivolumab in advanced solid cancers. Cancer Treat Rev [Internet]. 2018;70(July):75–87. Available from: https://doi.org/10.1016/j.ctrv.2018.08.001

78. Rivera SC, Kyte DG, Aiyegbusi OL, Slade AL, McMullan C, Calvert MJ. The impact of patient-reported outcome (PRO) data from clinical trials: A systematic review and critical analysis. Health Qual Life Outcomes. 2019;17(1):1–19.

79. Kluetz PG, Slagle A, Papadopoulos EJ, Johnson LL, Donoghue M, Kwitkowski VE, et al. Focusing on core patient-reported outcomes in cancer clinical trials: Symptomatic adverse events, physical function, and disease-related symptoms. Clin Cancer Res. 2016;22(7):1553–8.

80. European Medicines Agency. Qualification of novel methodologies for drug development: guidance to applicants. [cited 2022 Feb 13]; Available from: www.ema.europa.eu/contact

81. Division of Clinical Outcome Assessment, U.S. Food and Drug Administration. Roadmap to Patient-Focused Outcome Measurement in Clinical Trials (text version) | FDA [Internet]. 2018 [cited 2022 Feb 14]. Available from: https://www.fda.gov/drugs/drug-development-tool-ddt-qualification-programs/roadmap-patient-focused-outcome-measurement-clinical-trials-text-version

82. U.S. Food and Drug Administration. Qualification Process for Drug Development Tools Guidance for Industry and FDA Staff [Internet]. 2020 Nov [cited 2022 Feb 14]. Available from: https://www.fda.gov/vaccines-blood-biologics/guidance-compliance-regulatory-information-biologics/biologics-

83. U.S. Food and Drug Administration. FDA Patient-Focused Drug Development Guidance Series for Enhancing the Incorporation of the Patient's Voice in Medical Product Development and Regulatory Decision Making [Internet]. 2020 [cited 2022 Feb 14]. Available from: https://www.fda.gov/drugs/development-approval-process-drugs/fda-patient-focused-drug-development-guidance-series-enhancing-incorporation-patients-voice-medical

84. U.S. Food and Drug Administration. Patient-Focused Drug Development Guidance

Public Workshop: Incorporating Clinical Outcome Assessments into Endpoints for Regulatory Decision-Making. Discussion Document. 2019; Available from: https://www.fda.gov/media/132505/download

85. Janssens R, Huys I, Van Overbeeke E, Whichello C, Harding S, Kübler J, et al. Opportunities and challenges for the inclusion of patient preferences in the medical product life cycle: A systematic review. BMC Med Inform Decis Mak. 2019;19(1):1–16.

86. Bouvy JC, Cowie L, Lovett R, Morrison D, Livingstone H, Crabb N. Use of Patient Preference Studies in HTA Decision Making: A NICE Perspective. Patient [Internet]. 2020;13(2):145–9. Available from: https://doi.org/10.1007/s40271-019-00408-4

87. Whichello C, Bywall KS, Mauer J, Stephen W, Cleemput I, Pinto CA, et al. An overview of critical decision-points in the medical product lifecycle: Where to include patient preference information in the decision-making process? Health Policy (New York). 2020;124(12):1325–32.

88. U.S. Food and Drug Administration. Patient Preference Information – Voluntary Submission, Review in PMAs, HDE Applications, and De Novo Requests and Inclusion in Decision Summaries and Device Labeling: Final Guidance. 2016; Available from: http://www.fda.gov/downloads/Training/CDRHLearn/UCM522377.pdf

89. Ho M, Saha A, McCleary KK, Levitan B, Christopher S, Zandlo K, et al. A Framework for Incorporating Patient Preferences Regarding Benefits and Risks into Regulatory Assessment of Medical Technologies. Value Heal. 2016;19(6):746–50.

90. Medical Device Innovation Consortium. Medical Device Innovation Consortium (MDIC) Patient Centered Benefit-Risk Project Report: A Framework for Incorporating Information on Patient Preferences Regarding Benefit and Risk into Regulatory Assessments of New Medical Technology. 2015.

91. Huls SPI, Whichello CL, van Exel J, Uyl-de Groot CA, de Bekker-Grob EW. What Is Next for Patient Preferences in Health Technology Assessment? A Systematic Review of the Challenges. Value Heal [Internet]. 2019;22(11):1318–28. Available from: https://doi.org/10.1016/j.jval.2019.04.1930

92. Crossnohere NL, Fischer R, Crossley E, Vroom E, Bridges JFP. The evolution of patient-focused drug development and Duchenne muscular dystrophy. Expert Rev

Pharmacoecon Outcomes Res [Internet]. 2020 Jan 2;20(1):57–68. Available from: https://www.tandfonline.com/doi/full/10.1080/14737167.2020.1734454

93. Hazlewood GS. Measuring Patient Preferences: An Overview of Methods with a Focus on Discrete Choice Experiments. Rheum Dis Clin North Am [Internet]. 2018;44(2):337–47. Available from: https://doi.org/10.1016/j.rdc.2018.01.009

94. Flythe JE, West M. Using patient preference information to inform regulatory decision making an opportunity to spur patient-centered innovation in kidney replacement therapy devices. Clin J Am Soc Nephrol. 2021;16(4):642–4.

95. Myeloma UK, National Institute for Health and Care Excellence. Measuring Patient Preferences: An exploratory study to determine how patient preferences data could be used in health technology assessment (HTA) - Project report. 2019.

96. Soekhai V, Whichello C, Levitan B, Veldwijk J, Pinto CA, Donkers B, et al. Methods for exploring and eliciting patient preferences in the medical product lifecycle: a literature review. Drug Discov Today [Internet]. 2019;24(7):1324–31. Available from: https://doi.org/10.1016/j.drudis.2019.05.001

97. Meara A, Crossnohere NL, Bridges JFP. Methods for measuring patient preferences: An update and future directions. Curr Opin Rheumatol. 2019;31(2):125–31.

98. Johnson FR, Zhou M. Patient Preferences in Regulatory Benefit-Risk Assessments: A US Perspective. Value Heal. 2016;19(6):741–5.

99. Holmes EAF, Plumpton C, Baker GA, Jacoby A, Ring A, Williamson P, et al. Patient-Focused Drug Development Methods for Benefit–Risk Assessments: A Case Study Using a Discrete Choice Experiment for Antiepileptic Drugs. Clin Pharmacol Ther. 2019;105(3):672–83.

100. Wortley S, Flitcroft K, Howard K. What is the role of community preference information in health technology assessment decision making? A case study of colorectal cancer screening. Int J Technol Assess Health Care. 2015;31(4):241–8.

101. Ho MP, Gonzalez JM, Lerner HP, Neuland CY, Whang JM, McMurry-Heath M, et al. Incorporating patient-preference evidence into regulatory decision making. Surg Endosc [Internet]. 2015;29(10):2984–93. Available from: http://dx.doi.org/10.1007/s00464-014-4044-2

102. Katz EG, McNulty P, Levitan B, Treichler P, Martynowicz J, Jamieson C. U.S. Food and

Drug Administration’s Patient-Focused Drug Development Initiative: Experience with Integration of Patient-Experience Data in a New Drug Application for Esketamine Nasal Spray Plus a Newly Initiated Oral Antidepressant for Treatment-Resistant. Ther Innov Regul Sci [Internet]. 2022;56(1):38–46. Available from: https://doi.org/10.1007/s43441-021-00340-6

103. Mühlbacher AC, Bridges JFP, Bethge S, Dintsios CM, Schwalm A, Gerber-Grote A, et al. Preferences for antiviral therapy of chronic hepatitis C: a discrete choice experiment. Eur J Heal Econ. 2017;18(2):155–65.

104. Mühlbacher AC, Juhnke C, Beyer AR, Garner S. Patient-Focused Benefit-Risk Analysis to Inform Regulatory Decisions: The European Union Perspective. Value Heal [Internet]. 2016;19(6):734–40. Available from: http://dx.doi.org/10.1016/j.jval.2016.04.006

105. Tegenge MA, Moncur MM, Sokolic R, Forshee RA, Irony T. Advancing the science of patient input throughout the regulatory decision-making process. Learn Heal Syst. 2017;1(3):1–6.

106. European Medicines Agency. EMA Regulatory Science to 2025: Strategic Reflection. 2020;1–79. Available from: https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/ema-regulatory-science-2025-strategic-reflection_en.pdf

107. European Medicines Agency. Benefit-Risk Methodology Project [Internet]. [cited 2022 May 7]. Available from: https://www.ema.europa.eu/en/about-us/what-we-do/regulatory-science-research/benefit-risk-methodology

108. PREFER. Patient Preferences [Internet]. [cited 2022 May 7]. Available from: https://www.imi-prefer.eu/

109. Innovative Medicines Initiative. PREFER: Case study catalogue. 2020.

110. Janssens R, Lang T, Vallejo A, Galinsky J, Plate A, Morgan K, et al. Patient Preferences for Multiple Myeloma Treatments: A Multinational Qualitative Study. Front Med [Internet]. 2021 Jul 6;8(July):1–17. Available from: https://www.frontiersin.org/articles/10.3389/fmed.2021.686165/full

111. Auclair D, Mansfield C, Fiala MA, Chari A, Cole CE, Kaufman JL, et al. Preferences and Priorities for Relapsed Multiple Myeloma Treatments Among Patients and Caregivers in the United States. 2022;(March):573–85.

112. Kvam AK, Waage A. Health-related quality of life in patients with multiple myeloma-does it matter? Haematologica. 2015;100(6):704–5.

113. Gries KS, Fastenau J, Seo C, Potrata B, Iaconangelo C, Serrano D. Development of the Multiple Myeloma Symptom and Impact Questionnaire: A New Patient-Reported Outcome Instrument to Assess Symptom and Impacts in Patients With Multiple Myeloma. Value Heal [Internet]. 2021;24(12):1807–19. Available from: https://doi.org/10.1016/j.jval.2021.06.010

114. Nathwani N, Bell J, Cherepanov D, Sowell FG, Shah R, McCarrier K, et al. Patient perspectives on symptoms, health-related quality of life, and treatment experience associated with relapsed/refractory multiple myeloma. Support Care Cancer [Internet]. 2022;30(7):5859–69. Available from: https://doi.org/10.1007/s00520-022-06979-7

115. Tremblay G, Daniele P, Breeze J, Li L, Shah J, Shacham S, et al. Quality of life analyses in patients with multiple myeloma: results from the Selinexor (KPT-330) Treatment of Refractory Myeloma (STORM) phase 2b study. BMC Cancer. 2021;21(1):1–10.

116. International Agency for Research on Cancer. World Health Organization. Multiple Myelom Factsheet - Global Cancer Observatory [Internet]. 2020 [cited 2022 Aug 7]. Available from: https://gco.iarc.fr/today/data/factsheets/cancers/35-Multiple-myeloma-fact-sheet.pdf

117. Despiégel N, Touboul C, Flinois A, Saba G, Suzan F, Gonzalez-McQuire S, et al. Health-Related Quality of Life of Patients With Multiple Myeloma Treated in Routine Clinical Practice in France. Clin Lymphoma, Myeloma Leuk [Internet]. 2019;19(1):e13–28. Available from: https://doi.org/10.1016/j.clml.2018.08.019

118. Jagannath S, Mikhael J, Nadeem O, Raje N. Digital Health for Patients With Multiple Myeloma: An Unmet Need. JCO Clin Cancer Informatics. 2021;(5):1096–105.

119. van der Poel MWM, Oerlemans S, Schouten HC, van de Poll-Franse L V. Elderly multiple myeloma patients experience less deterioration in health-related quality of life than younger patients compared to a normative population: a study from the population-based PROFILES registry. Ann Hematol [Internet]. 2015 Apr 5;94(4):651–61. Available from: http://link.springer.com/10.1007/s00277-014-2264-0

120. Bahlis NJ, Siegel DS, Schiller GJ, Samaras C, Sebag M, Berdeja J, et al. Pomalidomide, dexamethasone, and daratumumab immediately after lenalidomide-based treatment in

patients with multiple myeloma: updated efficacy, safety, and health-related quality of life results from the phase 2 MM-014 trial. Leuk Lymphoma [Internet]. 2022;63(6):1407–17. Available from: https://doi.org/10.1080/10428194.2022.2030477

121. Hungria V, Beksac M, Weisel KC, Nooka AK, Masszi T, Spicka I, et al. Health-related quality of life maintained over time in patients with relapsed or refractory multiple myeloma treated with daratumumab in combination with bortezomib and dexamethasone: results from the phase III CASTOR trial. Br J Haematol. 2021;193(3):561–9.

122. Martino M, Rossi M, Ferreri A, Loteta B, Morabito A, Moscato T, et al. Quality of life outcomes in multiple myeloma patients: a summary of recent clinical trials. Expert Rev Hematol [Internet]. 2019 Aug 3;12(8):665–84. Available from: https://doi.org/10.1080/17474086.2019.1634541

123. LeBlanc MR, Hirschey R, Leak Bryant A, LeBlanc TW, Smith SK. How are patient-reported outcomes and symptoms being measured in adults with relapsed/refractory multiple myeloma? A systematic review. Qual Life Res [Internet]. 2020 Jun 17;29(6):1419–31. Available from: http://link.springer.com/10.1007/s11136-019-02392-6

124. Staccini P, Lau AYS, Editors S, Yearbook I. Social Media , Research , and Ethics : Does Participant Willingness Matter ? Findings from the 2020 International Medical Informatics Association (IMIA) Yearbook of Medical Informatics , Section on Consumer Health Informatics and Education. 2020;176–83. Available from: thesis

125. Fifer SJ, Ho K, Lybrand S, Axford LJ, Roach S. Alignment of preferences in the treatment of multiple myeloma – a discrete choice experiment of patient, carer, physician, and nurse preferences. BMC Cancer [Internet]. 2020 Dec 11;20(1):546. Available from: https://bmccancer.biomedcentral.com/articles/10.1186/s12885-020-07018-6

126. Ludwig H, Moreau P, Dimopoulos MA, Mateos MV, Kaiser M, Hajek R, et al. Health-related quality of life in the ENDEAVOR study: carfilzomib-dexamethasone vs bortezomib-dexamethasone in relapsed/refractory multiple myeloma. Blood Cancer J [Internet]. 2019;9(3). Available from: http://dx.doi.org/10.1038/s41408-019-0181-0

127. LeBlanc MR, Bryant AL, LeBlanc TW, Yang Q, Sellars E, Chase CC, et al. A cross-sectional observational study of health-related quality of life in adults with multiple

myeloma. Support Care Cancer [Internet]. 2022;30(6):5239–48. Available from: https://doi.org/10.1007/s00520-022-06943-5

128. Rifkin RM, Bell JA, DasMahapatra P, Hoole M, Lowe M, Curran C, et al. Treatment Satisfaction and Burden of Illness in Patients with Newly Diagnosed Multiple Myeloma. PharmacoEconomics - Open [Internet]. 2020;4(3):473–83. Available from: https://doi.org/10.1007/s41669-019-00184-9

129. Engelhardt M, Ihorst G, Singh M, Rieth A, Saba G, Pellan M, et al. Real-World Evaluation of Health-Related Quality of Life in Patients With Multiple Myeloma From Germany. Clin Lymphoma, Myeloma Leuk [Internet]. 2021;21(2):e160–75. Available from: https://doi.org/10.1016/j.clml.2020.10.002

130. Sully K, Trigg A, Bonner N, Moreno-Koehler A, Trennery C, Shah N, et al. Estimation of minimally important differences and responder definitions for EORTC QLQ-MY20 scores in multiple myeloma patients. Eur J Haematol. 2019;103(5):500–9.

131. Crawford R, Gries KS, Valluri S, Fastenau J, Morrison R, Yeh TM, et al. The patient experience of relapsed refractory multiple myeloma and perspectives on emerging therapies. Cancer Rep. 2022;(January):1–8.

132. Cella D, McKendrick J, Kudlac A, Palumbo A, Oukessou A, Vij R, et al. Impact of elotuzumab treatment on pain and health-related quality of life in patients with relapsed or refractory multiple myeloma: results from the ELOQUENT-2 study. Ann Hematol. 2018;97(12):2455–63.

133. Efficace F, Cottone F, Sparano F, Caocci G, Vignetti M, Chakraborty R. Patient-Reported Outcomes in Randomized Controlled Trials of Patients with Multiple Myeloma: A Systematic Literature Review of Studies Published Between 2014 and 2021. Clin Lymphoma, Myeloma Leuk [Internet]. 2022;22(7):442–59. Available from: https://doi.org/10.1016/j.clml.2022.01.009

134. Richter J, Sanchez L, Biran N, Wang CK, Tanenbaum K, DeVincenzo V, et al. Prevalence and Survival Impact of Self-Reported Symptom and Psychological Distress Among Patients With Multiple Myeloma. Clin Lymphoma, Myeloma Leuk [Internet]. 2021;21(3):e284–9. Available from: https://doi.org/10.1016/j.clml.2020.11.021

135. Fernandes LL, Zhou J, Kanapuru B, Horodniceanu E, Gwise T, Kluetz PG, et al. Review of patient-reported outcomes in multiple myeloma registrational trials: highlighting areas

for improvement. Blood Cancer J [Internet]. 2021;11(8):1–6. Available from: http://dx.doi.org/10.1038/s41408-021-00543-y

136. Plesner T, Dimopoulos MA, Oriol A, San-Miguel J, Bahlis NJ, Rabin N, et al. Health-related quality of life in patients with relapsed or refractory multiple myeloma: treatment with daratumumab, lenalidomide, and dexamethasone in the phase 3 POLLUX trial. Br J Haematol. 2021;194(1):132–9.

137. Leleu X, Kyriakou C, Vande Broek I, Murphy P, Bacon P, Lewis P, et al. Prospective longitudinal study on quality of life in relapsed/refractory multiple myeloma patients receiving second- or third-line lenalidomide or bortezomib treatment. Blood Cancer J [Internet]. 2017;7(3). Available from: http://dx.doi.org/10.1038/bcj.2017.20

138. Abonour R, Rifkin RM, Gasparetto C, Toomey K, Durie BGM, Hardin JW, et al. Effect of initial treatment on health-related quality of life in patients with newly diagnosed multiple myeloma without immediate stem cell transplant intent: results from the Connect® MM Registry. Br J Haematol. 2021;193(1):93–100.

139. Abonour R, Wagner L, Durie BGM, Jagannath S, Narang M, Terebelo HR, et al. Impact of post-transplantation maintenance therapy on health-related quality of life in patients with multiple myeloma: data from the Connect® MM Registry. Ann Hematol. 2018;97(12):2425–36.

140. Selvy M, Kerckhove N, Pereira B, Barreau F, Nguyen D, Busserolles J, et al. Prevalence of Chemotherapy-Induced Peripheral Neuropathy in Multiple Myeloma Patients and its Impact on Quality of Life: A Single Center Cross-Sectional Study. Front Pharmacol. 2021;12(April):1–12.

141. Nikolaou A, Ambavane A, Shah A, Ma W, Tosh J, Kapetanakis V, et al. Belantamab mafodotin for the treatment of relapsed/refractory multiple myeloma in heavily pretreated patients: a US cost-effectiveness analysis. Expert Rev Hematol [Internet]. 2021;14(12):1137–45. Available from: https://doi.org/10.1080/17474086.2021.1970522

142. Chari A, Romanus D, DasMahapatra P, Hoole M, Lowe M, Curran C, et al. Patient-Reported Factors in Treatment Satisfaction in Patients with Relapsed/Refractory Multiple Myeloma (RRMM). Oncologist. 2019;24(11):1479–87.

143. Baz R, Lin HM, Hui AM, Harvey RD, Colson K, Gallop K, et al. Development of a conceptual model to illustrate the impact of multiple myeloma and its treatment on

health-related quality of life. Support Care Cancer. 2015;23(9):2789–97.

144. He J, Duenas A, Collacott H, Lam A, Gries KS, Carson R, et al. Patient Perceptions Regarding Multiple Myeloma and Its Treatment: Qualitative Evidence from Interviews with Patients in the United Kingdom, France, and Germany. Patient - Patient-Centered Outcomes Res [Internet]. 2021 Sep 9;14(5):613–23. Available from: https://doi.org/10.1007/s40271-021-00501-7

145. Postmus D, Richard S, Bere N, Valkenhoef G Van, Galinsky J, Low E, et al. Individual Trade-Offs Between Possible Benefits and Risks of Cancer Treatments : Results from a Stated Preference Study with Patients with Multiple Myeloma. Oncologist. 2018;44–51.

146. Wilke T, Mueller S, Bauer S, Pitura S, Probst L, Ratsch BA, et al. Treatment of relapsed refractory multiple myeloma: which new PI-based combination treatments do patients prefer? Patient Prefer Adherence [Internet]. 2018 Nov;Volume 12:2387–96. Available from: https://www.dovepress.com/treatment-of-relapsed-refractory-multiple-myeloma-which-new-pi-based-c-peer-reviewed-article-PPA

147. Lassalle A, Thomaré P, Fronteau C, Mahé B, Jubé C, Blin N, et al. Home administration of bortezomib in multiple myeloma is cost-effective and is preferred by patients compared with hospital administration: results of a prospective single-center study. Ann Oncol [Internet]. 2016 Feb;27(2):314–8. Available from: https://doi.org/10.1093/annonc/mdv563

148. National Health Council. Measuring Patient Experiences: Distinguishing Between Patient-Reported Outcomes and Patient Preferences [Internet]. [cited 2022 Aug 28]. Available from: https://nationalhealthcouncil.org/webinars/coa-series-measuring-patient-experiences-distinguishing-between-patient-reported-outcomes-and-patient-preferences/

149. Reaney M, Rodriguez AM. Patient Experience Information: Streamlining and Harmonizing the Collection of Patient Preference and Patient-Reported Outcomes Data. Pharmaceut Med [Internet]. 2020 [cited 2022 Aug 27];34(5):309–14. Available from: https://doi.org/10.1007/s40290-020-00356-7

150. Boutin M, Dewulf L, Hoos A, Geissler J, Todaro V, Schneider RF, et al. Culture and Process Change as a Priority for Patient Engagement in Medicines Development. Ther Innov Regul Sci. 2017;51(1):29–38.

151. Patient Focused Medicines Development. Patient Engagement for Medicines Development [Internet]. 2021 [cited 2022 Jun 15]. Available from: https://patientfocusedmedicine.org/

152. Deane K, Delbecque L, Gorbenko O, Hamoir AM, Hoos A, Nafria B, et al. Co-creation of patient engagement quality guidance for medicines development: An international multistakeholder initiative. BMJ Innov. 2019;5(1):43–55.

153. Patient Focused Medicines Development. Patient Engagement Management Suite [Internet]. 2021 [cited 2022 Jun 19]. Available from: https://pemsuite.org/

154. Patient Focused Medicines Development. Patient Engagement Quality Guidance [Internet]. 2018 [cited 2022 Jun 19]. Available from: https://patientfocusedmedicine.org/peqg/patient-engagement-quality-guidance.pdf

155. Feldman D, Kruger P, Delbecque L, Duenas A, Bernard-Poenaru O, Wollenschneider S, et al. Co-creation of practical "how-to guides" for patient engagement in key phases of medicines development—from theory to implementation. Res Involv Engagem. 2021;7(1):1–11.

156. Patient Focused Medicines Development. Patient Engagement Synapse - The global patient engagement map and network [Internet]. [cited 2022 Jun 19]. Available from: https://patientengagement.synapseconnect.org/

157. EUPATI. Patient Engagement Roadmap [Internet]. [cited 2022 Jul 3]. Available from: https://toolbox.eupati.eu/resources-guidance/patient-engagement-roadmap/

158. Innovative Medicines Initiative. FACILITATE. Available from: https://facilitate-project.eu/

159. EUPATI. Ongoing Projects [Internet]. Available from: https://eupati.eu/projects/

160. Innovative Medicines Initiative. FACILITATE [Internet]. [cited 2022 Jul 14]. Available from: https://facilitate-project.eu/

161. EUPATI. Ongoing Projects [Internet]. [cited 2022 Jul 14]. Available from: https://eupati.eu/projects/

162. Warner K, See W, Haerry D, Klingmann I, Hunter A, May M. EUPATI guidance for patient involvement in medicines research and development (R and D); Guidance for pharmaceutical industry-led medicines R and D. Front Med. 2018;5(OCT):1–8.

163. Hunter A, Facey K, Thomas V, Haerry D, Warner K, Klingmann I, et al. EUPATI guidance for patient involvement in medicines research and development: Health technology assessment. Front Med. 2018;5(SEP):231.

164. Haerry D, Landgraf C, Warner K, Hunter A, Klingmann I, May M, et al. EUPATI and patients in medicines research and development: Guidance for patient involvement in regulatory processes. Front Med. 2018;5(AUG):1–11.

165. Klingmann I, Heckenberg A, Warner K, Haerry D, Hunter A, May M, et al. EUPATI and patients in medicines research and development: Guidance for patient involvement in ethical review of clinical trials. Front Med. 2018;5(SEP):251.

166. Innovative Medicines Initiative. PARADIGM [Internet]. [cited 2022 Jul 2]. Available from: https://imi-paradigm.eu/

Appendices

A1. Examples of Patient Engagement Initiatives

1. Patient Focused Medicines Development (PFMD) Initiative

PFMD is an international multistakeholder initiative composed of patients, patient organizations, the pharmaceutical industry, regulators, HTA bodies, and national advisory organizations established in 2015 to facilitate and advance patient engagement across the MPLC (150,151).

This global coalition is synergizing efforts to develop a more effective approach to integrate patient experience in medicines development and approval pathways by developing a standardized framework, among the necessary tools, guidance, and resources to support its adoption/implementation across stakeholders and stages of the medical product lifecycle.

To streamline patient engagement, PFMD has outlined four priority areas to be addressed: 1) culture and process change, 2) development of a standardized framework, 3) information exchange, 4) and training. Table 1 provides further insight into this matter.

Table 1. Priorities to advance patient engagement (150,152).

Priorities	**Rationale**	**Examples of previous work/initiatives**	**PFMD planned or ongoing activities**
Culture and process change	Culture and process change are vital to ensure routine implementation of patient engagement activities. Sharing examples of good practice and tangible benefits of effective patient engagement (and conversely, communicating the disadvantages of ineffective or inexistent patient engagement) will lead to a	- Boutin *et al.* present several case study examples of patient engagement and benefits from patient organizations and from the pharmaceutical industry. - Several funding bodies already require or encourage the submission of plans for	PFMD initiative will expectedly provide guidance, resources, and support to overcome process barriers and drive meaningful patient engagement.

	change in attitudes and beliefs that will motivate the consistent implementation of patient engagement. The use of incentives can also be a powerful motivator for change.	patient engagement in product research, development, and approval processes in order to obtain funding.	
Development of a standardized framework	Various frameworks have been published. However, they have only partially addressed the MPLC and while complementary, they result in a fragmented patient engagement guidance that lacks continuity and consistency among stakeholders.	- Clinical Trials Transformation Initiative recommendations - FDA's Patient Focused Drug Development (PFDD) Conceptual Framework - National Health Council/ Genetic Alliance Framework - PCORI engagement rubric - FasterCures Value Framework - National Institute for Health Research (UK NIHR) INVOLVE recommendations[1]	PFMD is currently developing a global meta-framework building on existing frameworks and recommendations to facilitate effective and systematic patient engagement across medicines' development lifecycle.
Information exchange	An efficient mechanism for accessing and sharing aggregated information on ongoing and planned patient	European Patients' Academy (EUPATI) developed a *PatientInvolved*	PFMD has launched an information exchange platform that maps patient engagement

	engagement activities will allow stakeholders to access and share experiences and good practices, provide a practical means to share opportunities for patient engagement, and prevent duplication of effort and resource waste.	webpage listing research and development projects in which patients can be involved.	activities to facilitate information and knowledge exchange among patient engagement stakeholders and to disclose partnership opportunities.
Training	Effective patient engagement activities require specific skills and knowledge from all stakeholders involved.	- EUPATI provides training courses and educational materials for patients and patient organizations.	PFMD provides a training platform for all patient engagement stakeholders. This coalition is also preparing a series of master classes to address training needs and focus areas informed by stakeholders.

PFMD is following a four-step approach to building a framework for patient engagement: (1) mapping the patient engagement landscape through an extensive literature review and analysis of existing frameworks and initiatives; (2) arranging multistakeholder workshops and interviews to identify their needs and preferences on patient engagement; (3) refinement of tools to develop and pilot a draft meta-framework for patient engagement and (4) creation of the final framework and implementation tools (151,152). The result is the Patient Engagement Management Suite (PEM Suite), comprising a set of practical tools and guidance to help stakeholders plan, assess and execute patient engagement activities in a systematic, efficient, and meaningful manner. Figure 1 depicts the features of the PEM Suite.

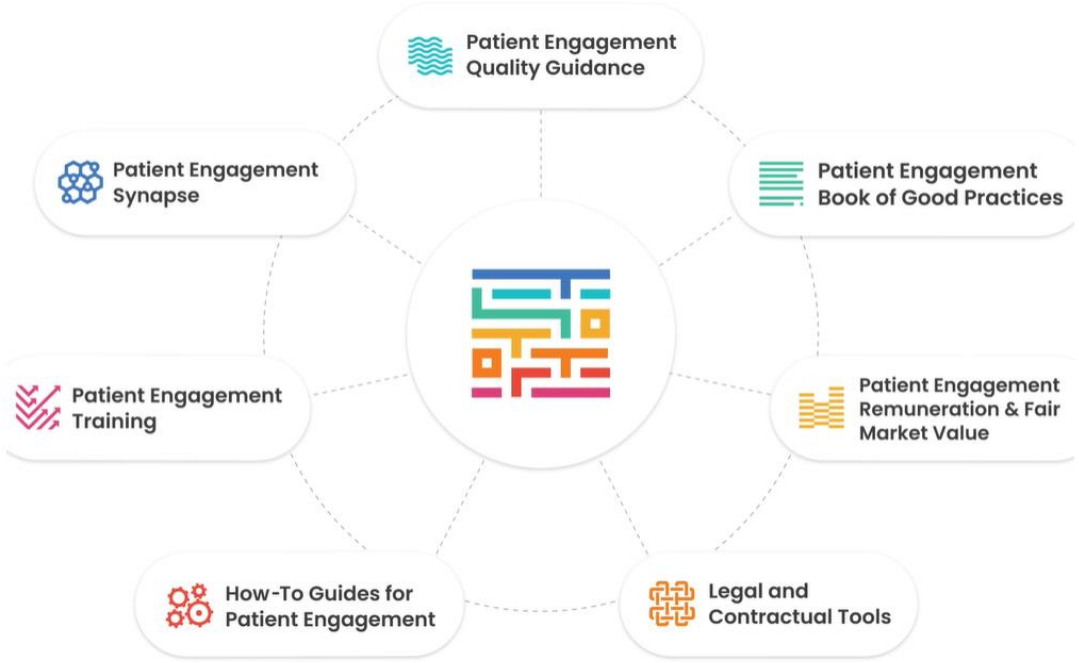

Figure 1. Overview of the Patient Engagement Management Suite. Retrieved from Patient Focused Medicines Development website (151)

- **Patient Engagement Quality Guidance** (153,154)

The Patient Engagement Quality Guidance is a practical guide for planning, developing, and assessing the quality of patient engagement activities throughout the development and lifecycle of medicines (as well as medical devices). This guidance introduces seven quality measures or principles that a good patient engagement project should consider. Figure 2 presents an overview of the set of patient engagement quality criteria (154).

This tool can be used to guide the planning and development of a patient engagement project, to assess the quality and impact of ongoing or completed patient projects, and for gap analysis, *i.e.*, to identify areas for improvement, missed opportunities and their impact, which can help plan future patient engagement projects. Therefore, the Quality Guidance Tool presents two versions for different scenarios: (1) planning a project, and (2) assessing an ongoing or finalized project (154).

Figure 2. Overview of the Patient Engagement Quality Criteria. Retrieved from Patient Focused Medicines Development website (151)

- **Book of Good Practices** (153)

PFMD created the Book of Good Practices to supplement the Patient Engagement Quality Guidance with a selection of examples from positive real-world patient engagement initiatives. The selection was based on the Patient Engagement Quality Guidance so that the chosen initiatives present two or more of the seven Quality Criteria. This document will be annually updated.

- **Practical How-to Guides for Patient Engagement** (153,155)

These tools provide further tailored guidance for the implementation of patient engagement on specific patient engagement activities across the medicines development lifecycle that were not covered in previous guidance or with the necessary detail.

The following guidance documents have been issued:

- How-To Guide for Patient Engagement in the Early Discovery and Preclinical phases;
- How-to Guide on patient engagement in the development of a COA strategy;
- How-to Guide on patient engagement in clinical trial protocol design;

- Plain language summaries of peer-reviewed publications and conference presentations: practical ‘How-To’ Guide for multi-stakeholder co-creation;
- Guidance for Community Advisory Boards;
- Guidance for Patient Engagement in Early Dialogues (HTA).

- **Patient Engagement Training** (153)

PFMD has launched a comprehensive training program, accredited by the Accreditation Council for Medical Affairs (ACMA), for anyone wishing to start or advance their patient engagement knowledge. The following modules are now available:

- Patient Engagement Basics: 15-minute introduction to patient engagement (level 1)
- Patient Engagement Value: What is patient engagement and how to get it right (level 1)
- Patient Engagement in Practice: Your first step to making it happen (level 2)
- Patient Engagement Training and Resources Repository: A selection of 140 reviewed patient engagement training courses and educational materials (level 3)

More advances modules are currently underway.

- **Patient Engagement Remuneration & Fair Market Value** (153)

This project intends to assist fair remuneration of the patient community for interacting with the pharmaceutical industry through patient engagement activities by driving the adoption of remuneration standards. PFMD working group is developing a trusted process for fair remuneration.

- **Legal and Contractual Tools** (153)

Since creating a legal agreement ‘from scratch’ between patient advocates and the industry can be a challenging task, PFMD has established guiding principles for the development of reasonable legal agreements and contracts. Additionally, the working group has published reference templates to facilitate even more this task. There is also an explained version of the guiding principles document, and of each reference agreement, providing extra information regarding descriptions of the terminology, clauses, sections, and rationale, for anyone who

needs to gain a better understanding of this matter. Finally, PFMD has made tools available to help manage competing interests and conflicts of interest when planning or conducting a patient activity project.

- **Patient Engagement Synapse** (153,156)

SYNaPsE (SYNergising Patient Engagement) is a digital platform designed to collect and map patient engagement initiatives, frameworks, organizations, events, experts, training materials, and other resources.

- **Additional PFMD activities and initiatives**:
    - **Patient Engagement Open Forum**: consists of a series of virtual events (once every quarter) aiming to provide a place where the patient engagement community can catalyse patient engagement by fostering collaboration and co-creation (151).
    - **Patient Engagement in Digital Health and Data**: PFMD wants to build knowledge on patient engagement standards for digital health and data, towards better patient-centred digital health outcomes and impact through the involvement of patients: (1) review learnings from patient engagement in medicine and medical device development, (2) validation of findings and co-creation of patient engagement standards in digital, (3) call to action for implementation of systematic patient engagement in digital health, and (4) dissemination of patient engagement best practices and support for implementation (151).

2. <u>European Patients' Academy on Therapeutic Innovation (EUPATI)</u>

EUPATI is a multi-stakeholder public-private partnership originally launched by the IMI-EUPATI project (2012-2017) and today established as an independent non-profit. EUPATI visions that patients are key stakeholders in improving medicines development. For this reason, EUPATI works on improving patient engagement through patient education. It provides training courses, workshops, and educational materials to empower patients and patient organizations with the skills and knowledge required to effectively contribute to medicines research and development (R&D).

- **EUPATI Patient Engagement Roadmap**

This roadmap offers a structured approach for patient involvement in medicines' R&D which highlights specific opportunities for patient engagement throughout the four key stages of the medicines' R&D lifecycle and offers concrete examples. This tool is expected to facilitate patient engagement and stimulate further discussion (157). The roadmap is presented in figure 3.

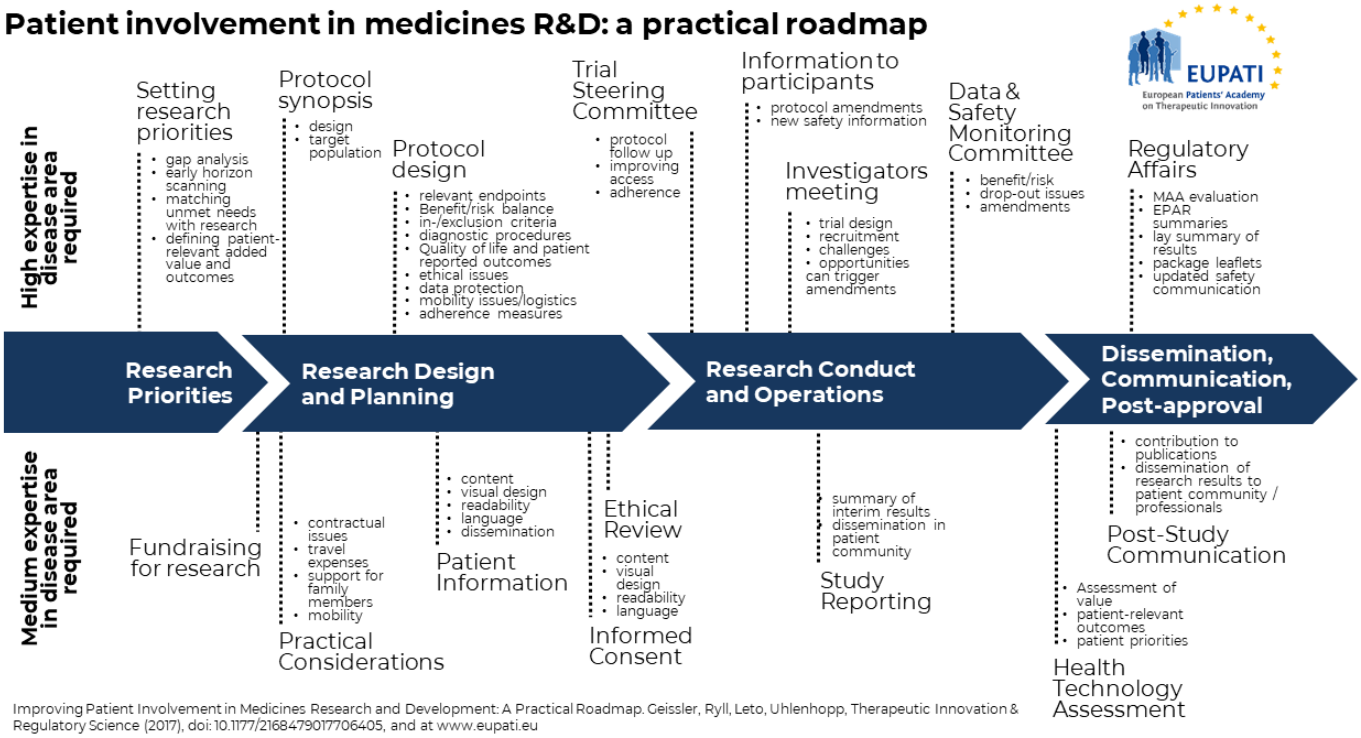

Figure 3. Patient Engagement Roadmap. Retrieved from EUPATI (157).

- **Patient Engagement Current Initiatives**

HTA Patient Involvement (158,159)

At the beginning of 2022, the European Federation of Pharmaceutical Industries and Associations launched and funded the 360° HTA Patient Involvement initiative to investigate the current methods and processes for patient involvement in HTA in Europe and how they are perceived by the different stakeholders. This initiative will review those methods and processes and develop best practices.

EUPATI has been a part of this project (together with patient organizations, and pharmaceutical industries), by contributing to the survey on the role of patient engagement in HTA and gathering responses.

IMI-FACILITATE (160,161)

FACILITATE (which stands for "framework for clinical trial participants' data reutilisation for a fully transparent and ethical ecosystem") was launched at the beginning of 2022 by the IMI as a 4-year project whose mission is: 1) to enable clinical trial participants to access their data generated during the studies so that it can be used for shared medical decision-making with their health professionals, 2) and then to create a process that allows data to be re-used in future research. In other words, this project aims to develop an innovative data-sharing and re-use process that allows access and portability of patient data within a General Data Protection Regulation (GDPR) compliant framework. The project is being conducted by a consortium of 27 partners, including EUPATI.

First, FACILITATE will develop an ethical, legal, and regulatory framework with clear rules on how patients' data should be accessed, used, and reused (*e.g.*, recommendations on which, when, and how data should be returned to study participants, or how this data can be used in health care decision making and/or future research). Afterwards, this project will develop the necessary technological solutions to implement sharing and reuse of patient data towards a more effective, safer, and faster medicines development.

- **EUPATI Guidance**

In 2018, EUPATI has issued a set of four guidance documents to support the implementation of patient engagement among the key stakeholders and across the MPLC. Each guidance recommends working methods and processes and suggests specific activities and areas that hold opportunities for patient involvement.

Guidance for Patient Involvement in Industry-Led Medicines R&D (162)

This guidance originated from the current lack of guidance on patient involvement able to comprehensively cover the full scope of medicines R&D. It is aimed at the pharmaceutical industry that wants to engage patients in R&D activities and provides recommendations for

ground rules and suggestions for the integration of patient engagement across the whole process of medicines R&D. The document draws on previous guidance (which are named in the document) and is intended to provide a groundwork for a future code of practice for the pharmaceutical industry.

First, the guidance outlines the reasons why there is a need for clear guidance on patient engagement in R&D activities. Then, it presents areas and specific activities in R&D where patient involvement can take place. Further on, the document suggests work practices for fostering meaningful and effective patient engagement. For example, pre-engagement discussions are vital for ensuring mutually beneficial interaction, adequate preparation, and agreement on specific details. All these considerations should be defined in a written agreement, namely the objectives, type of interaction, consent, release, confidentiality, compensation, data privacy, compliance, declaration of conflict, and timelines. The guidance also suggests ways to identify patients for engagement activities (*e.g.*, through existing patient organizations, or advertisement), further discusses compensation for patients involved in activities, and highlights the importance of transparency on patient engagement (by making public collaboration opportunities between companies and patients/patient organizations and joining efforts among stakeholders to build expertise on this novel area).

Guidance for Patient Involvement in HTA (163)

This guidance covers the interaction between HTA bodies and patients or patient organizations in the context of HTA. First, the guidance provides background information about the European scenario on patient engagement in HTA. This document is based on recent published research and examples of good practices from individual HTA bodies. Particularly, it builds on a set of values identified by the HTAi, an international society aimed at fostering HTA, which are relevance, fairness, equity, legitimacy, and capacity building. These values are further described in the guidance document and are the starting point for the recommendations on working practices for HTA bodies and patient organizations so that both parties can meet those values.

Then, the guidance presents suggestions of patient involvement activities for HTA organizations, which are organized in three categories: 1) outreach and education (*e.g.*, communication about roles for patients and their impact, holding meetings in public, and providing glossaries), 2) wider involvement (*e.g.*, including patients as committee lay

members), 3) and resource provision (*e.g.*, developing peer support groups for involved patients).

Finally, the guidance presents an overview of the progress and barriers to patient engagement in HTA. Examples of the former include: the HTAi Patient and Citizen Involvement Interest Group (PCIG) which is working on setting a comprehensive and searchable platform of publicly available resources to help patients participating in HTA processes; a "framework for action" for public and patient involvement in HTA issued for a Canadian HTA organization. Identified barriers to patient engagement in HTA include lack of financial compensation, poor training and support, and low general awareness.

Guidance for Patient Involvement in Regulatory Processes (164)

This EUPATI guidance covers patient involvement in the regulatory field, and it is aimed at regulatory authorities who wish to engage patients in their activities. The guidance is expected to streamline regulators' efforts to implement effective patient engagement. It starts with a description of the evolving, yet heterogeneous, landscape of patient engagement in regulatory activities at the European level.

This guidance was built upon the EMA's previous work and experiences which shows that patient involvement in regulatory activities can result in increased transparency and trust in regulatory processes and mutual respect between regulators and patients/patient organizations. Yet, for this to be materialized, the guidance authors propose a set of objectives for effective patient involvement in medicines regulation that can only be attained through close collaboration between all stakeholders involved. Moreover, effective patient involvement requires a solid and widely accepted patient engagement framework, and therefore, this guidance document presents key elements for developing one.

The guidance also suggests working practices for patient participation in regulatory authorities' activities, based on the EMA framework for interaction:

- A network of patient organizations (potentially in collaboration with other regulatory authorities).
- A forum of exchange with patient organizations established within the regulatory authority.

- Creation of a pool of individual patients expert in their disease and its treatment to facilitate patient involvement in medicines evaluation and information.
- Interaction particularly in the field of communication for information dissemination.
- A program of actions for capacity-building, focusing on training and raising awareness about the regulatory system.
- Financial support for patients contributing to the regulator's activities.

Further on, the guidance recommends establishing an agreement between all parties prior to each interaction. All these considerations should be defined in a written agreement, namely the objectives, type of interaction, consent, release, confidentiality, compensation, data privacy, compliance, declaration of conflict, and timelines.

Furthermore, it explains how patients can participate in regulatory activities (*i.e.,* as members, individual experts, representatives of a specific organization, or observers). For this matter, the authors recommend establishing eligibility criteria. Accordingly, the guidance provides eligibility criteria for patient organizations when interacting with regulators.

Finally, this document discusses compensation for patients involved in activities and highlights the importance of monitoring after implementation of such activities through a public annual report on interactions (the document defines which aspects should be included in the report).

Guidance for Patient Involvement in Ethical Review of Clinical Trials (165)

This guidance is directed to all stakeholders involved in the ethical review of clinical trials. It provides recommendations for ground rules and suggestions to facilitate patient involvement in ethics committees. It covers what is needed to be considered when implementing patient involvement, namely: the timing and nature of patient involvement in ethical reviews, the patient's level of expertise, and conditions for patient involvement in ethics committees (written agreements, transparency, representativeness, and compensation). This document also presents a roadmap where patient involvement may occur in ethical reviews of clinical trials. The recommendations provided in this guidance aim to define the most suitable type of patient expertise needed and to guide ethics committees to adapt their processes to effectively engage with patients.

- **Matchmaking - EUPATIConnect**

EUPATI has developed a matchmaking service called EUPATIConnect that helps collaboration between members of the EUPATI partnership, by bringing EUPATI patient experts and researchers together. EUPATI patient experts can enroll in this platform where they are asked to indicate their availability to participate in various projects, and at the same time, researchers can submit their requests to find patients with the needed knowledge to partner up with them in their projects. In turn, EUPATI is responsible for connecting both parties.

3. PARADIGM (Patients Active in Research and Dialogues for an Improved Generation of Medicines)

In 2018, the IMI launched the PARADIGM project, a 30-month public-private partnership across 34 organizations, co-led by the European Patients' Forum (EPF) and the European Federation of Pharmaceutical Industries and Associations (EFPIA). This project mission was to advance "structured, effective, meaningful, ethical, innovative, and sustainable patient engagement" throughout the MPLC for better health outcomes (166).

The project's proposed to explore the needs and perspectives of the different stakeholders involved in the medicines' development process. Through the insight gathered and the gaps identified, PARADIGM developed a set of tools and guidance (building upon existing tools and initiatives, such as PFMD and EUPATI) for three key-decision making points: research priority setting, design of clinical trials, and early dialogue (166).

As a result, PARADIGM launched a toolbox that gathers all the project's recommendations, as well as a set of comprehensive tools and practices to facilitate patient engagement. These tools are organized into three groups: planning patient engagement; conducting patient engagement; and reporting and evaluation. Figure 4 provides an overview of the PARADIGM toolbox (166).

Figure 4. Overview of the PARADIGM toolbox. Retrieved from the IMI PARADIGM website (166).

A2. Search Queries

Search query for patient experience data:

("patient experience data"[tiab] OR "patient engagement"[tiab] OR "patient and public involvement"[tiab] OR "patient involvement"[tiab] OR "patient-generated health data"[tiab] OR "Patient-Focused Drug Development"[tiab] OR "patient focused medicines development"[tiab] OR "patient perspective"[tiab]) AND ("drug* development"[tiab] OR "medicine* development"[tiab] OR "clinical care"[tiab] or "health technology assessment"[tiab] OR HTA[tiab] OR "regulatory"[tiab] OR "medical product life cycle"[tiab])

Search query for PROs:

"patient reported outcome*"[tiab] AND ("regulatory"[tiab] OR "HTA"[tiab] OR "health technology assessment"[tiab] OR "medical product lifecycle"[tiab] OR "clinical research"[tiab] OR "clinical trial*"[tiab] OR "drug* approval*"[tiab] OR "medicine* approval*"[tiab] OR "clinical care")

Search query for patient preferences:

"patient preference*"[tiab] AND ("regulatory" OR "HTA" OR "health technology assessment" OR "medical product lifecycle" OR "discrete choice experiment"[tiab])

Search query for PROs in multiple myeloma:

("patient Reported outcome*" OR HRQL OR HRQOL OR "health related quality of life") AND "Multiple Myeloma"

Search query for patient preferences in multiple myeloma:

("patient preference*" OR "trade-off*" OR "discrete choice experiment") AND "Multiple Myeloma"