How-To Guides for Patient Engagement

PATIENT FOCUSED MEDICINES DEVELOPMENT

‘How-To’ Guide on patient engagement in the development of a Clinical Outcome Assessment (COA) strategy

The guides are part of the **Patient Engagement Management Suite** - a hub for effective and practical patient engagement.

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Introduction and overview of the work

Patient Focused Medicines Development (PFMD) partners with patients to design and improve global healthcare. PFMD focuses on making patient engagement a systematic reality by co-creating much-needed resources that enable all stakeholders to embark on and enhance their patient engagement journey.

PFMD involved multi-stakeholder working groups (including the patient community, representatives from the pharmaceutical industry and contract research organizations, external consultants with the relevant experience and expertise) in developing the How-to Guides series[1]. These How-to Guides build on the Patient Engagement Quality Guidance (PEQG[2,3]) tool and provide **step-by-step recommendations** to **involve patient partners** in specific activities and/or phases in the treatment[4] development continuum. Each Guide functions as a standalone tool but can also be easily combined with the other Guides to form a comprehensive roadmap for patient engagement activities.

The following How-to Guides are currently available:

- How-to Guide for Patient Engagement in the Early Discovery and Preclinical phases
- How-to Guide on Patient Engagement in Clinical Trial Protocol Design.
- Plain language summaries (PLS) of peer-reviewed publications and conference presentations: practical 'How-To' Guide for multi-stakeholder co-creation.

This guidance aims to provide a basis for more meaningful and systematic engagement of patient partners at each of the critical milestones in the COA strategy development.

This How-to Guide aims to provide a basis for more meaningful and systematic patient engagement in the development of a COA strategy within clinical trials.

[1] Access at: https://pemsuite.org/how-to-guides/

[2] The Patient Engagement Quality Guidance can support the preparation and planning of a partnership in the development of a COA Strategy. The seven criteria of the PEQG have been adapted to fit the scenarios, type of activities, and stakeholders involved. The Patient Engagement Quality Guidance (PEQG) has two scenarios with respective considerations; scenario 1 for planning PE activities and scenario 2 for assessing ongoing and completed projects for their PE quality. Link to scenario 1 (planning PE): http://patientfocusedmedicine.org/peqg/patient-engagement-quality-guidance-scenario-1.pd

[3] Deane, K., Delbecque, L., Gorbenko, O. et al. on behalf of the PFMD Patient Engagement Meta-framework Co-creation Team. Co-creation of patient engagement quality guidance for medicines development: an international multi stakeholder initiative. *BMJ Innovations* 2019;5:43-55.

[4] Please, consider that **treatment** is used throughout this How-to Guide to refer to drugs, as well as to medical technologies.

How was it developed?

The Guide is a true example of co-creation, having involved 29 multi-stakeholder contributors, including patient experts, the pharmaceutical industry, clinical research organizations, and external consultants with the relevant experience and expertise in the activity. Each draft of this particular How-To Guide was reviewed internally, tested and agreed upon by the group, and further validated during external consultations.

The Patient Engagement Quality Guidance (PEQG)[5] is proposed as a reference in planning and preparing for involving patient partners in the process of adopting a patient-focused COA strategy. The seven Criteria of the PEQG have been specially adapted to fit the scenarios, type of activities, and stakeholders involved.

Who is this guide for?

This How-to Guide will be of use to all stakeholders eager to begin or continue meaningful patient engagement at all stages of the **treatment-**development process. This guide has been developed for stakeholders that already have a medium to advanced understanding of COA measures.

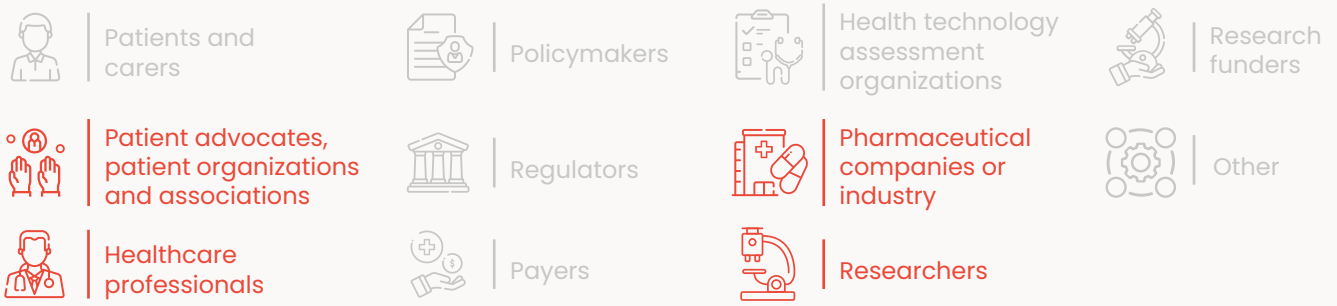

Figure 1. Relevant stakeholders in patient engagement in the development of a Clinical Outcomes Assessment (COA) strategy

To facilitate the understanding of this How-to Guide for readers who do not have background knowledge of COA, we would suggest reviewing the resources in Annex 2 - Resources and tools.

[5] Access at: https://pemsuite.org/peqg/

How to use this How-to Guide?

This How-to Guide should always be used in a relevant and applicable manner to the project at hand. This How-to Guide (as with all PFMD How-to Guides) has been built to be used alongside the PFMD Patient Engagement Quality Guidance (PEQG), which defines seven Quality Criteria for good patient engagement. The PEQG should be used as a reference in setting up partnerships, planning, and preparing for involving patients as partners in your research. The seven Quality Criteria can help consider others' expectations and manage them.

This How-to Guide is organized around eight steps that outline key moments and aspects for patient engagement in the development of a Clinical Outcomes Assessment (COA) strategy, including:

- **Step 1 - Preparations for Setting up Partnership and Collaboration:**

  This step focuses on the definition of engagement goals to prepare for meaningful collaboration. It includes identifying, selecting, and inviting patient partners for the partnership activities and the co-development of a pre-engagement plan.

- **Step 2 -Building a Partnership for Optimal Patient Engagement:**

  This step focuses on defining the scope, expectations, and project timelines for a beneficial partnership, including the methods and formats for the patient engagement activities. It also considers other stakeholders that can be involved to understand patients' perspectives and drive successful outcomes from patient engagement.

- **Step 3 -Identification of Relevant Disease-related Concepts:**

  This step focuses on the identification and understanding of the **symptoms** and treatment burden patients experience and how these affect their day-to-day function and **quality of life**. This will ensure that the COA measure(s) selected or developed (see steps 4 & 5) include the **concept(s)** relevant and important to patients and/or carers in the situations (contexts) where the measures will be used.

- **Step 4 -Assessing the Suitability of COA Measures:**

  This step focuses on assessing existing COA measures to determine if any offer acceptable (methodologically rigorous) coverage of the **concept(s)** for the key domains of interest.

- **Step 5 -COA Adoption, Adaptations and Development:**

  This step explains what happens if no existing measure is relevant to the **target population** and **context of use.** The adaptation of an existing measure or the development of a new measure should be considered.

- **Step 6 -COA Implementation within Clinical Trials:**

  This step focuses on the critical role that patient partners can play in reviewing the proposed clinical trial **protocol.** Focusing specifically on COA **endpoints,** feasibility for the trial participants to complete the COA as described in the **protocol,** the modality of COA administration, and its language and readability.

- **Step 7 -COA Data Interpretation:**

  This step provides information on the interpretation of COA data and how patient insights can

provide a valuable perspective on what constitutes **clinically meaningful change** for COAs.

- **Step 8 -COA Communication:**

  This step focuses on improving the clarity and meaningfulness of communications around COA data considered important; so that patients and HCPs can understand and use the data collected in the clinical trials to inform their decisions.

Figure 2. How-to Guide on Patient Engagement in the development of a Clinical Outcomes Assessment (COA) Strategy

The technical terms (in **bold red text**) have a definition in the Glossary section.

Context

This comprehensive guidance is focused on patient engagement in developing and implementing a **Clinical Outcome Assessment (COA)** strategy. A COA strategy includes the identification, implementation, interpretation, and communication of COA in the context of clinical trials. Although the importance of the patient perspectives in COAs is becoming more recognized, clear guidance of how to embed this perspectives in design and tactical execution of a COA strategy is still missing. This How-to Guide builds on the existing COA Guidance from FDA, EMA, ISOQOL, and ISPOR and provides clear guidelines for meaningful patient engagement throughout the process.

Clinical Outcome Assessment (COA)[7] is an essential component of clinical trial design. The patient (and/or carer) and clinician perspective on the patient experience and **treatment benefits** and **risks** are obtained. Consideration of the patient partners' perspective is increasingly required by regulatory authorities, **health technology assessment** (HTA) bodies, health care professionals (HCP), and patients in decision-making. Therefore, its measurement, interpretation, and integration to COA, as well as its communication necessitates careful planning and quality assurance.

The appropriate development of a **fit-for-purpose** COA measure is an iterative process that includes patient partners, HCP, and key opinion leaders' input. Principles pertaining to how COA measures should be developed and validated, and how **patient experience data** should be analyzed and interpreted, are well-established. The FDA COA guidance is specific to the context of using COA to support labeling claims. Additionally, the FDA has recently undertaken the development of patient-focused drug development guidance documents with the aim of showing stakeholders how to adequately collect and submit **patient experience data** and other relevant information for medical product development and regulatory decisions. The importance of involving patient

[6] Please check the References section to access the list of Guidance documents.

[7] There are four types of Clinical Outcome Assessments: Patient Reported Outcomes (PRO) measures, Observer-reported Outcome (ObsRO) measures, Clinical Reported Outcomes (ClinRO) measures and Performance Outcome (PerfO) measures. See Glossary for definitions.

[8] Food and Drug Administration. (2009) Guidance for Industry. Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims. Available at: https://www.fda.gov/media/77832/download

[9] Food and Drug Administration. (2020) Patient-Focused Drug Development: Collecting Comprehensive and Representative Input Guidance for Industry, Food and Drug Administration Staff, and Other Stakeholders. Available at: https://www.fda.gov/media/139088/download

Food and Drug Administration. (2019) Patient-Focused Drug Development: Methods to Identify What Is Important to Patients Guidance for Industry, Food and Drug Administration Staff, and Other Stakeholders. Available at: https://www.fda.gov/media/131230/download

Food and Drug Administration. (2019) Incorporating Clinical Outcome Assessments into Endpoints for Regulatory Decision-Making. Public Workshop Dec 2019 Available at: https://www.fda.gov/media/132505/download

Food and Drug Administration. (2018) Patient-Focused Drug Development: Collecting Comprehensive and Representative Input. Available at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/patient-focused-drug-development-collecting-comprehensive-and-representative-input

Food and Drug Administration. (2018) Patient-Focused Drug Development Guidance: Methods to Identify What is Important to Patients and Select, Develop or Modify Fit-for-Purpose Clinical Outcome Assessments.Meeting October 2018 Available at: https://www.fda.gov/drugs/news-events-human-drugs/patient-focused-drug-development-guidance-methods-identify-what-important-patients-and-select

partners in the development of COA measures to capture **concepts** that are relevant and meaningful to patients is well acknowledged in these references. However, many elements need to be considered beyond the **COA** instrument itself in a clinical trial to demonstrate the patient-perceived value of a treatment to authorities, payor, clinicians, and patients.

These other elements include, but are not limited to: the design of the trial, trial **endpoints**, relevance of the COA according to the targeted population (e.g., health literacy level, culture, language), timing of the COA assessments, trial staff training, and the interpretation of the COA results and their dissemination. These are all elements of a COA strategy. Some of these aspects are usually discussed with the regulatory (and sometimes **HTA**) authorities, with very limited (if any) input from patient partners. However, engaging with patient partners to discuss these aspects is crucial not only to ensure that the COA instruments included in the trial are relevant and **fit-for-purpose** but also to allow a meaningful implementation, interpretation, and communication of the COA data. How to concretely engage with patient partners throughout these aspects will be covered throughout this document.

Why is it important to involve patient partners in COA decision making?

Example from a real case:

A Pharmaceutical Company has conducted a Phase III clinical trial using two Patient-Reported Outcomes Measures (PROM), one generic and one specific for the disease. The generic PROM was chosen because the pharma company had conducted research and found out that such PROM had been used most frequently in clinical trials. The disease specific PROM was selected because the company was focusing on particular **symptoms** of the disease.

Result: The generic PROM did not indicate an improvement in perceived health status.

The outcomes measured through the disease specific PROM indicated that patients taking the new drug maintained a stable **Quality of Life**.

What went wrong?

- The generic PROM was not sensitive enough to measure outcomes that reflect the specific needs of the specific patient population. Therefore, the measure is not **fit-for-purpose** in that specific trial design.
- The patient population had not been stratified for specific **symptoms** and therefore, patients who did not experience the **symptoms** under investigation had been included in the PRO reporting. Hence, the effect on specific patient relevant **symptoms** attenuated in the overall results measured as an average effect across the entire patient population.

Conclusion: By not engaging patient partners from the beginning to understand what is important to patients, the pharma company chose a PROM that was not suited for the population enrolled in the clinical trial. Selection of the right PROMs informed by patient partners can support demonstrating meaningful change in the right concepts.

Step 1
Preparations for Setting up Partnership and Collaboration

Figure 3. Step 1 of the How-to Guide

The **objective** of this step is to:

- **Define partnership and collaboration goals** to prepare for a meaningful, effective, and respectful interaction with patient partners to build a mutually beneficial partnership.
- **Identify, select and invite patient partners** for the partnership activities and prepare your research team.

Establishing meaningful long-term relationships, understanding patient partners' views on collaboration with sponsors, and recognizing the value for both groups are critical to successful collaborations in medicines R&D. The timing of the initial interaction and the steps leading up to it are both critical.

1.1. Define partnership and collaboration goals

There are different ways in which initial conversations about patient engagement in clinical trials may arise between patient partners and sponsors. Sponsors may have a specific project or program where they wish to seek input from patients.

A patient organization may be looking for opportunities for its members to shape the direction of drug development. Opportunities may also arise out of existing patient engagement partnerships in other stages of drug development. A key part of identifying opportunities is having an open and honest conversation about the purpose of working together and what each stakeholder hopes to achieve. Stakeholders should work together to scope ideas and opportunities and agree on a shared purpose for the collaboration.

Even if the sponsor has pre-defined the scope of the collaboration, they should still, when possible, discuss and define each step with the patient partners.

1.2. Identify, select and invite patient partners

Identify patient partners

This step bridges the gap between patient organizations and sponsors to set the stage for the selection of suitable patient partners. Patient organizations know their patients and thus can often recommend to sponsors patient advocates who may be interested in participating. However, the objective of the collaboration may sometimes require partnership with various profiles of patients to approximate the representability of the global population.

Brief checklist for identifying a list of potential patient partners:

- The type of patient partner profile needed (i.e., 'naive' patient, patient advocate, patient expert, carer or family member, patient community).
- The level of research expertise the patient partner should have (and if any training or education may be needed).
- The role the patient partner will take and how complex it is. (See the description of the four levels of patient partner contribution below)
- The patient partner's medical condition profile.
- The patient partner's ability to mobilize their community. For example, what is the scope, and geographical footprint of their network?
- Other capabilities and competencies needed from the patient partner[10].

To meaningfully conduct a patient engagement activity, the right patient partners need to be identified. Patient organizations - where they exist - are the first and key point of contact to identify individuals and/or experts to engage to ensure the right match for the right activity.

The patient organization and sponsors should also consider respective capacity to partner:

- Does the infrastructure allow to set up a partnership easily? Or would support be needed to make collaboration happen?
- Are the project timelines, expected duration, frequency of interactions, and technology used feasible?

See 'Patient engagement in medicines development: Recommendations on how to find the right match for the right patient engagement activity.' to support identifying the right patient partners[11]. See also the National Health Council (NHC) document "Tackling Representativeness"[12].

[10] Access at: http://imi-paradigm.eu/PEtoolbox/pe-capabilities/

[11] Access via: PARADIGM. (2020) Patient engagement in medicines development: Recommendations on how to find the right match for the right patient engagement activity. Available at: https://synapse.pfmd.org/resources/patient-engagement-in-medicines-development-recommendations-on-how-to-find-the-right-match-for-the-right-patient-engagement-activity, pages 9-10

[12] NHC "Tackling Representativeness". Available at: https://nationalhealthcouncil.org/wp-content/uploads/2019/12/Representativeness%20in%20Patient%20Engagement.pdf

Selecting and inviting patient partners

Initiating the partnership is about establishing contact between the sponsor and the patient partners. Establishing the relationship gives teams time to prepare. The patient partner will need time to understand the project and to build trust in the sponsor. Equally, the sponsor will need time to build trust, as well as understand its capacity and interest to deliver.

When deciding the best time to set up a sponsor–patient partnerships in research, apply the general principle of 'as early as possible'. Ideally, establish contacts a year before embarking on the development of a Clinical Outcomes Assessment strategy, especially if the patient partner side has no prior experience and needs to be trained. Equally, all industry contributors need to be trained on the value of patient engagement and how to engage patients[13].

Taking careful consideration of the patient partners to collaborate with and avoiding selection bias are both very important. Select patient partners who value independence and who can review and advise the sponsor's strategy objectively from the viewpoint of the patients they represent.

Approach a registered patient organization. While a 'naive' individual patient perspective may be beneficial at times, engaging individuals without ties to a patient organization may lead to input that is not representative of the patient community.

Patient partner diversity is also important, including from a geographical perspective. The patient experience can vary from Western to Eastern Europe, for example, and choosing a single patient from Western Europe is likely to lead to some perspectives being left out.

Depending on the context or in case of no existing patient organizations in the field of interest, patient pools or networks that are organized around public institutions may provide a good reference to patient experts to engage in research projects. For example, the European Patients Academy (EUPATI) provides a matchmaking service to connect with patient experts[14].

When initiating contact with selected patient partners, a brief description of the role of the patient partner to be involved in the project should be prepared in advance, outlining the expected level of contribution. This role description can later be co-developed and shaped further with input from patient partners in Step 2.

Initial contact before developing a pre-collaboration plan should facilitate confirming the patient partners interest, explain and agree on goals and expectations, establish transparency (for what will the research team use the information obtained through the partnership/collaboration, why it is important to obtain patient input, ensure the patient partner would make a good candidate for project participation, etc.) and establish a co-creation relationship.

[13] Patient Engagement Training, an innovative learning program that will concretely help you start your patient engagement journey or take it to the next level. Available here: https://pemsuite.org/patient-engagement-training/

[14] European Patients Academy (EUPATI, 2000 (https://collaborate.eupati.eu/)

Step 2
Building a Partnership for Optimal Patient Engagement

Figure 4. Step 2 of the How-to Guide

The **objective** of this step is to:

- **Define the scope, expectations, and project timelines** for a mutually agreed and beneficial partnership.
- **Define the methods and formats** for the patient engagement activities.
- Consider **involving others in the partnership activities** to understand patients' perspectives and drive successful outcomes from patient engagement.

This step sets out the process for the successful initiation of a patient engagement partnership. The key principles of patient engagement can be openly discussed and further applied (see Annex 1 - PE Quality Guidance), including also practical considerations of the patient partners' perspective and preparing them for an optimal project kick-off.

Building a respectful partnership between patients and sponsors will help build the trust that is critical to successful collaborations in treatment research and development. Patient partners' involvement should not simply be a 'tick-box' exercise for regulatory approval. The trust built in this step could potentially lead to a long-term relationship that can effectively support communication around the project itself, the recruitment and retention plan for a clinical trial, and dissemination of the study results. Long-term partnerships with the patient community can also have a positive impact on a company's reputation, public trust in the company, and overall community willingness to partner.

2.1. Clarify the project plan and goals

Once mutual interest between patient partners and the sponsor has been established, further planning of activities and clarification of the goals of the collaboration for both partners need to be agreed.

Sponsors may refer to the PARADIGM EUPATI industry guidance and suggested working practices

or the National Health Council Rubric for Good Patient Engagement[15] as a practical tool to guide preparation and interactions when project planning with patient partners.

Patient partners and sponsors should address the following:

- Use of the Patient Engagement Quality Guidance[16] to help plan the project and engagement activities, collectively review the relevant considerations;
- Discuss and agree on the shared purpose within the research project and the stakeholders to be involved to reach the common goals and objectives;
- Commit to transparent, respectful, and continuous communication during the project;
- Ensure all partners recognize and understand the value they contribute and understand each other well; patients are experts in their condition and sponsors have the knowledge and expertise of the clinical trial process. Both add value.
- Define the responsibilities of all contributors and identify respective leaders for collaboration and define accountability to avoid multiple sources interacting in an uncoordinated way;
- Identify if sponsors and patient partners need additional support or capacity building to properly engage and collaborate. This may include training and education on clinical trials in general and, more specifically, on COAs and their design.

It will be helpful to define the following considerations from the outset of the collaboration:

- What impact will patient partners' inputs have on the overall project?
- What are the sponsors hoping to gain from patient engagement?
- How will the greater patient community benefit from the collaboration?
- How will partners work together with their respective experiences and knowledge?

The patient community needs to know how their input made a difference and how they influenced the decision-making, reporting, and dissemination process. Patient partners should also know when their input could not be considered and the reasons should be explained to them. Sponsors should be prepared to proactively provide feedback to patient partners.

2.2. Define the project timelines

Long-term relationships between sponsors and patient partners are desirable to create strong collaborations for ongoing research. However, short-term collaborations are sometimes the only option. The duration of the collaboration should be defined and key milestones agreed in advance. Whatever the length of the relationship, patient partners should be involved as much as possible at every stage of the treatment development process and the sponsor should manage their expectations throughout.

When the project ends, the relationship between the sponsor and patient partner may continue through ongoing communication. Create a communication plan and define the structure, content, governance, and duration in advance.

[15] Access at: http://imi-paradigm.eu/PEtoolbox/EUPATI/PARADIGM-Suggested-Working-Practices.pdf and at: https://nationalhealthcouncil.org/wp-content/uploads/2019/12/NHC_Patient_Engagement_Rubric.pdf

[16] Access at: https://pemsuite.org/peqg/

Considerations for resources and time required

Patient partners

- Setting up partnerships might take time and resources from patient organizations in many aspects: identifying the right partners for projects, setting up processes for patients to be involved, and defining contractual needs just to name a few. In addition, sponsors might be struggling with tight deadlines which in turn might translate into unrealistic timeline expectations towards patient partners and patient engagement activities.
- It is important for patient partners to understand that research might take time and resources and projects might extend beyond the original estimates. Whatever the case, concerns should be possible to voice at any time during the project; either to the sponsors or patient organizations involved.

Sponsors

- Ensure to have the necessary resources required to support patient engagement activities - consider the people, time, and funding needed to engage with patient partners.
- Share the project plan and timelines with the patient partners so they can prepare for the collaboration. Do not underestimate the amount of time needed for administrative aspects, such as agreeing on contracts, and compliance processes. Involve the people needed for these tasks early in the process to avoid delays where delays are inevitable, and ensure clear communication with the patient partners within the project.

  This will increase the likelihood that they will contribute valuable ideas and critical observations for the development of the COA strategy.

2.3. Contracting considerations

The sponsor-patient partner relationship is often defined and governed by a legal agreement or contract. In some instances, an additional Confidentiality Agreement (CDA) is required if the topics covered in the patient engagement activities are commercially sensitive to the sponsor. Needless to say, all contractual arrangements must comply with the legal framework in the region or country concerned.

Once the patient partners have been identified and the project scope, roles, and responsibilities, are defined the contracting process can begin. The legal agreement will outline aspects such as compensation and reimbursement, among other things.

Sponsors may use the checklist below as a guide and should also consider if patient partners may require legal support, should they need it. Any problems[17] and anxiety experienced during this phase can be alleviated by an honest and straightforward conversation about the process and potential difficulties.

[17] For more information, review the resources co-created through the PFMD Patient Engagement Remuneration & Fair Market Value project: https://pemsuite.org/fmv/ and Patient Engagement Compensation and Contracting Toolbox developed for use in the USA by the National Health Council.

[18] See Survey by WECAN. WECAN (2018) Guiding Principles on Reasonable Agreements between Patient Advocates and Pharmaceutical Companies. Available at: https://wecanadvocate.eu/wp-content/uploads/2019/03/Guiding-Principles_final-document6.2_clean.pdf

Resources:

The use of co-created guides and agreements will also help to focus contracts on the essential elements and can support understanding and negotiating legal agreements. These include:

- Legal and Contracting tools, compiled by PFMD
- Guiding Principles on Reasonable Agreements between Patient Advocates and Pharmaceutical Companies, developed by the Workgroup of European Cancer Patient Advocacy Networks (WECAN), Myeloma Patients Europe and PFMD
- Patient Engagement Agreements Explained for collaborations between the patient community and stakeholders in healthcare systems, developed by IMI PARADIGM
- Patient Engagement Compensation and Contracting Toolbox developed for use in the USA by the National Health Council.

Checklist: Questions for sponsors to consider when setting up a contact between patient partners and sponsors	Comments/Notes
Has my organization worked with this patient/patient organization before? If yes, Have we previously had a contract in place for collaboration, can this speed up the contracting process? » Are there considerations around confidentiality, and if so, is a confidentiality agreement needed, or can this be covered within the contract?	
If no, Connect with the legal, compliance, data privacy teams to enquire about the time required to set up contracts » Relay this information to patient partners	
» What is the time required to review contracts for the partners?	
» Are the contracts fit for this collaboration and understandable? Check the co-created guidelines and agreements	
» Are there considerations around confidentiality, and, if so, is a confidentiality agreement needed or can this be covered within the contract?	

Checklist: Questions for sponsors to consider when setting up a contact between patient partners and sponsors	Comments/Notes
Is there internal guidance for reimbursing and compensating patient partners? (If no, review the PFMD PE Remuneration & FMV Project resources[19] and refer to the PFMD National Health Council's Patient Engagement Compensation and Contracting Toolbox[20] and the Guiding Principles on Legal Agreements[21])	
» Discuss reimbursement and compensation with patient partners and the potential implications if they accept compensation (e.g., impact on benefits, taxation)	
» Discuss the potential costs for the patient partners and how they will be reimbursed (e.g., are they paid up front or for each time they travel?)	
» Discuss with the patient partners the time and effort required to be involved in the project (e.g., preparation time, meetings, travel, independent work, reporting, and other communication as relevant)	
Have the lead times and deadlines been defined and agreed with the patient partner(s)?	
Have the roles and responsibilities and other rules of collaboration been defined with the patient partner(s)?	

2.4. Managing expectations and other considerations

It is important that patient partners are aware that clinical research is usually a lengthy process. Frequently, the results of early clinical research mean that the next steps of **clinical development,** and ultimately the launch of a new **treatment** or health care solution, may not happen. It is equally

[19] PFMD Patient Engagement Remuneration & Fair Market Value project: https://pemsuite.org/fmv/

[20] For more information: NHC. Patient Engagement Compensation and Contracting Toolbox. Available from: https://nationalhealthcouncil.org/patient-engagement-compensation-and-contracting/ (For USA)

[21] See section 8 on WeCAN. (2018) "Financial compensation and reimbursement of expenses" Available at: https://wecanadvocate.eu/wp-content/uploads/2019/03/Guiding-Principles_final-document6.2_clean.pdf

important that sponsors are aware that engaging patient partners requires proper resources and time input.

Put in place a predetermined plan with a clear communication plan to manage expectations if the medicine fails. Considering the potential psychological impact of this and maintaining trust among the stakeholders are crucial.

Considerations for managing expectations

- Consider whether your patient partners would benefit from a basic introduction to or training in medicines research and development before the collaboration project begins. This might include typical timeframes for each phase, understanding of COA and related strategy, and patient partner inclusion in a clinical development program.
- Establish an understanding of where the development of a COA strategy fits into the overall development of a product, and how patient partners can have an impact.
  - Even if the clinical trial does not progress to the next clinical stage, patient partners need to know that their involvement in the design was still important, and that all results generate useful insights that will help clinical research in the future.
- Patient organizations should explore whether capacity building or an orientation meeting with sponsors would be useful for preparing patient partners for a meaningful collaboration.
- Accommodate a wide range of views and ideas from all stakeholders involved.
  - Patient organizations may have their own view and that may or may not coincide with patient partners and other patient organizations.
  - No one can speak for all patients with a particular disease. Patient organizations need to make reasonable efforts to reflect a diversity of opinions.
- Consider global, multi-cultural feedback as views can vary depending on region/language/customs in different areas.
- Identify if sponsor research teams need to be trained on the value of the patient engagement and how to engage patients[20]

2.5. Deciding on the methods and formats for sponsor–patient partner interactions

Agree meeting rules and set out a clear goal at the start of each meeting.

[22] Patient Engagement Training, an innovative learning program that will concretely help you start your patient engagement journey or take it to the next level. Available here: https://pemsuite.org/patient-engagement-training/

Sponsor–patient partner relationships are founded on trust and ongoing transparent dialogue. There are different ways to interact for generating relevant and meaningful **insights.** Selecting interaction methods and formats that will deliver the outcomes based on the objectives of the patient engagement is important. Moreover, minimizing the burden on the patient community is crucial, as well as ensuring that their input is respected and acted upon.

Interaction formats

Partners should frequently assess whether the interaction method and formats are the best way to achieve the project objectives.

Checklist of practical considerations for patient engagement

- How frequently will the team meet? Where?
- How much time and effort does this require from patient partners in addition to the meetings?
- Are in-person meetings always necessary or are virtual meetings possible, and, if so, which platforms are used?
- Would communicating in English be a problem for some of the patient partners? If yes, how will it be managed?
- What burden does participating in meetings place on patient partners? (e.g. with regards to their health, for their carers, or impact on professional and private life)
- What costs for the patient partners are to be covered?
- Are the patient partner groups big enough that the meetings are not affected by last minute cancellations, but not too big that everyone has the opportunity to share their inputs?

Methods and approaches for patient engagement

There are several approaches to patient engagement that can be used to collect patient partner insights and inputs in the co-development of a COA strategy. Stakeholders can serve on ad hoc working groups to prioritize unanswered research questions, co-develop and review the COA strategy. They can also have more sustained involvement once the clinical trial begins, providing their input and guidance by serving on an advisory committee or a co-investigator. Much like the approaches, there is also variability with respect to the level or intensity in which partners are engaged. Engagement often occurs along a continuum ranging from stakeholder input, to consultation, to collaboration or shared leadership. A selection of different methods and approaches for patient engagement are introduced in the figure on the next page[23].

This selection of approaches need not to be viewed as mutually exclusive. An organization with fully developed patient engagement capacity is likely to rely on a variety of approaches combined to develop COAs collaboratively with patient partners. For example, a sponsor may establish a **Patient Advisory Board (PAB)** to oversee the entire development program within a disease area and may also attend **Community Advisory Boards (CAB)** for strategic input to the development program according to patient community priorities. Moreover, regular implementation of wider **surveys**

[23] For additional information please check the James Lind Priority setting partnerships guidance.

informed by **PAB** and **CAB** members' experiences and advice, in order to stay in touch with views of the patient population at large. Additionally, the sponsor may host focus groups or consult with a patient partner directly to tackle specific aspects in the development of a COA strategy.

Example of engagement type[24]	Description
Patient Advisory Boards / Community Advisory Boards	Live meeting. A single meeting or series of facilitated meetings to capture patient partners' perspectives, experiences and advice.
Interviews/Focus Groups	Live meeting. Provide deeper insight into patient partners' priorities, preferences and motivations and allow for elaborated conversation.
Surveys/Questionnaires	Engaging with patient partners in a live meeting or virtually via a series of questions/ratings to gain patient feedback.

For sponsors:

Consult internal knowledge and secondary data sources focused on patients and insights from previous patient engagement activities prior to engaging with patient partners to avoid duplication of effort and to build on insights and gaps previously identified.

The diverse approaches for involving patient partners in the development of a COA strategy vary, depending on the level of engagement. They range from gathering insights via surveys or consultation to shared leadership and partnership and can be used independently or simultaneously.

For patient partners:

When possible, do internal research on insights gathered in previous engagement activities with other sponsors (or even the same sponsor) and share these insights in a transparent dialogue.

2.6. Involving others in the partnership activities

Sponsors should consider which internal representatives need to be involved in or informed of engagement activities with patient partners and at what stage. This might include departments or functions such as: patient advocacy/engagement team, medical affairs, clinical operations, market access, regulatory affairs, health economics, psychometricians, PRO methodologists, epidemiologists, statisticians, legal and compliance teams.

- **Clinical research teams:** This includes relevant individuals in the sponsor organization that work on the clinical development program or clinical trial. It is important to consider if the

[24] Table elaborated from Transcelerate, Examples Methods of Engagement.
Available at: https://www.transceleratebiopharmainc.com/ppet/select-patients-appropriate-engagement-method/

clinical research team understands and recognizes the benefits of incorporating the learning from patient engagement, as well as how to incorporate patient insights into decision making.

- **Healthcare professionals (e.g. doctors, pharmacists, dentists, nurses):** This includes any trained health professional involved in the medical care of patients who may or may not be directly involved in research projects. Their role is to advise the sponsor team about clinical aspects of the condition, the current clinical practices including the aspects of patients management with a particular condition, feedback from patients to certain investigations and methods, and to share their experience in medicines development and public health policies.
- **Medicine and diagnostic solutions developers:** These include any public or private organization involved in research, development, manufacturing, marketing and/or distribution of medicinal products and/or other health products (i.e., medical devices, diagnostics and digital solutions). Their main role is as the sponsor of research projects, including development of COA strategy, and, if required, training for patients on these specific matters.
- **Contract research organizations and consultancy companies:** These organizations provide services related to clinical studies. They provide support for the sponsors and may act on their behalf to establish collaboration with patient partners. These partners should be trained on Patient Engagement to ensure they have the right approach.
- **Application builders, health literacy experts and digital experts:** These experts may be in charge of the development of services for patients in clinical research and development projects when relevant.

Step 3
Identification of Relevant Disease-Related Concepts

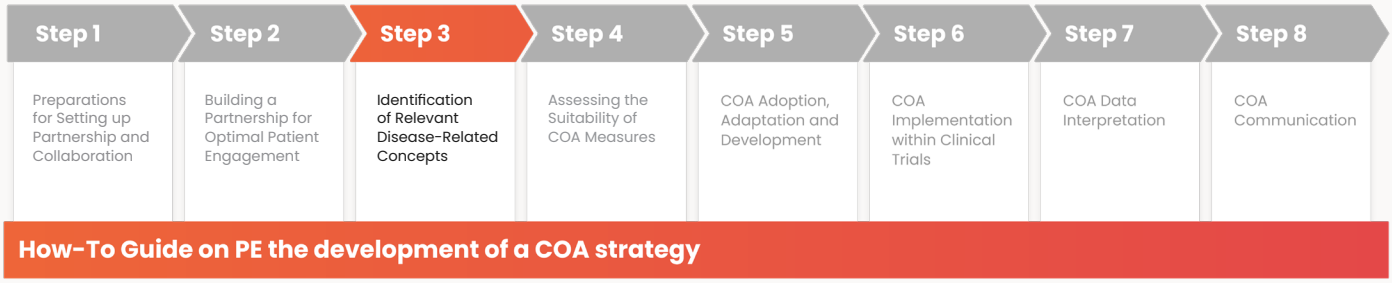

Figure 6. Step 3 of the How-to Guide

Patient's (and/or carer's) experience with a disease, its **treatment** and its impact on wellbeing is an essential starting point for any COA strategy.

The COA strategy must begin with the identification and understanding of the symptoms and treatment burden patients experience and how these affect their day-to-day function and **quality of life**. This will ensure that the COA measure(s) selected or developed include the **concept**(s) relevant and important to patients and/or carers in the situations (contexts) where the measures will be used[25].

3.1. What methods are commonly used for collecting patient partners' insights?

Community Advisory Boards/ Patient Advisory Boards

Interviews/Focus Groups

Surveys/Questionnaires

Figure 7. Methods for collecting patient partners' insights in Step 3.

[25] For more information please check the How-to Guide on How-to Guide for Patient Engagement in the Early Discovery and Preclinical phases, and specifically the section "Understanding the Condition type and therapy area". Available at: https://pemsuite.org/How-to-Guides/Early-Discovery.pdf

3.2. What specific information is provided?

Patient Partners can:

- Provide comprehensive and representative disease-specific input, such as **symptoms** of disease (e.g., frequency, severity, fluctuation, progression, chronicity, most bothersome, subpopulation differences and unmet needs, meaningful change), impacts of the disease on the patient's life and how they feel and function, and **treatment burden;** which potential impact(s) of a new **treatment** on **symptoms** and functioning will be most important for patients[26].

  Individual patients or carers have the unique direct experience in living with a condition or caring for someone living with a condition which they can share. They may or may not be part of a formal patient community or organization.
- Guide/review the design (e.g., input on the interview guide, **informed consent form, survey** questions, literature review **protocol**), implementation (e.g., recruitment, research feasibility), and interpretation of the qualitative/quantitative study and literature review.

Examples:

- Individual patients with a diagnosis of systemic lupus erythematosus (SLE) participated in face-to-face interviews. The findings from this study were intended to inform a comprehensive understanding of **patient experience** of SLE by confirming concepts of interest for measurement in future clinical trials.
- A **Patient Advisory Board** identified fatigue as a major symptom of Celiac Disease and as one that patients would want to be addressed by a **treatment** for their condition. Current Celiac PROMs address only gastro-intestinal symptoms that matter most to patients.

[26] For more information on structured preference methodology please check the following guidance documents:

Food and Drug Administration. (2020) Patient-Focused Drug Development: Collecting Comprehensive and Representative Input Guidance for Industry, Food and Drug Administration Staff, and Other Stakeholders. Available at: https://www.fda.gov/media/139088/download

Food and Drug Administration. (2018) Patient-Focused Drug Development Guidance: Methods to Identify What is Important to Patients and Select, Develop or Modify Fit-for-Purpose Clinical Outcome Assessments.Meeting October 2018 Available at: https://www.fda.gov/drugs/news-events-human-drugs/patient-focused-drug-development-guidance-methods-identify-what-important-patients-and-select

3.3. When does this step take place?

The research for the **identification of relevant concepts** should start as early as possible in the **treatment** development process and should be finalized before the start of a Phase 2 clinical trial. Ideally, a preliminary COA strategy (e.g., identification, implementation, interpretation, and communication of COA in the context of clinical trials) will be tested in Phase 2 and refined after Phase 2. The final COA strategy will be implemented in Phase 3[27].

Figure 8. Treatment development lifecycle and when the identification of relevant concepts takes place

[27] Based on FDA Guidance documents that you can find here.

Step 4
Assessing the Suitability of COA Measures

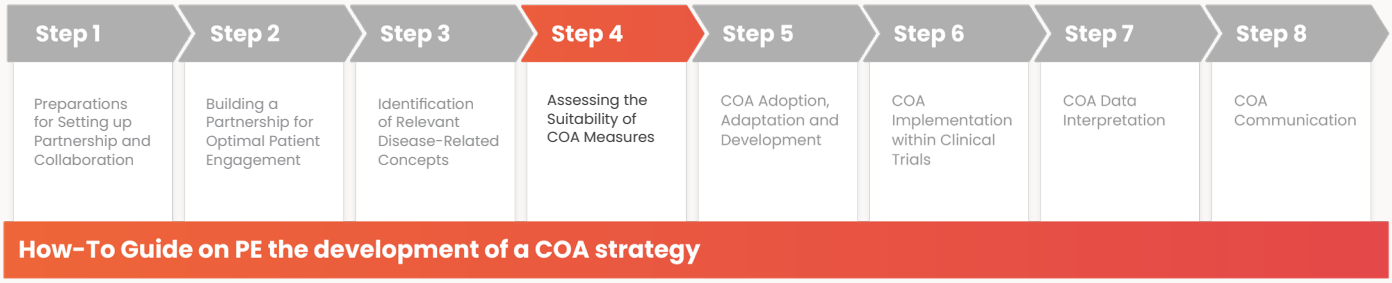

Figure 9. Step 4 of the How-to Guide

After identifying **concepts** that are clinically relevant, important to patients, and likely to be affected by the clinical trial **treatment,** the research team, in collaboration with patient partners, will review existing COA measures to determine which, if any, offers the best **concept** coverage for the key domains of interest. More specifically, the research team (including patient experts with experience in COA measures development) will determine the adequacy of the **concepts** covered. In addition, the research team will assess if the measure is appropriate for its intended use (e.g. clinical trial design, patient population, disease severity, etc.).

The **context of use** is an important aspect of COA measures development and describes detailed information about the patients it was designed for and what setting the tool will be used in[28]. A comprehensive review conducted by the research team is required to understand the measurement framework, and the content of the measure (i.e. how responses are captured and scored, and how often the data is collected).

This means ensuring that the trial and the COA measures encompass concepts important to them (as described in Step 3) —that the relevant disease **symptoms** are captured as well as how the disease and **treatment** impact patients' health related **quality of life**.

There are numerous COA measures available that measure a range of **concepts** from disease-specific **symptoms** and impacts to generic (i.e. non disease-specific) **health-related quality of life** outcomes. It is highly recommended that the patient partners who are involved during the COA suitability assessment stage confirm that the existing **measure**(s) selected for use within a clinical are indeed **fit-for-purpose** for them (as described in Step 3).

For example, measures that were developed previously without patient input may need review together with patient partners in order to ensure that the relevant **concept(s)** are measured. Other measures may be outdated due to medical progress or new standards of care. Tools developed without the appropriate patient input are at high-risk of scrutiny by regulators and high-risk of failure in detecting differences due to treatment.

[28] For more information please check: NHC Webinar on Successful COAs: It all Starts with the "Concept of Interest" and "Context of Use" available here: https://nationalhealthcouncil.org/coa-series-successful-coas-it-all-starts-with-the-concept-of-interest-and-context-of-use/

It is essential that COAs measure the **concepts** adequately for the target patient population. Additional work will be needed to assess the measurement properties of the instrument [29,30]. This ensures that the COA measurement properties are adequate and can capture changes in patient experience as a result of the clinical trial **treatment.**

If an existing COA measure is not **fit-for-purpose,** it may need to be revised with permission from the original developer. Without such permission, a new COA measure may need to be developed.

Case example: A patient partner acted as a consultant, reviewer, and contributor

Engagement Activities:

- Conference calls where the patient partner was an expert advisor
- Literature search and review informed by patient input
- Reporting back on topics driven by patient partner input

Key benefits:

- Insights and sources that would not otherwise have been identified
- Understanding the patient partner perspective directly
- Positive and worthwhile experience for research team and patient partner
- Sharing learnings for other projects optimal points of engagement

In some cases, not all **concepts** will be included in the COA measures in a clinical trial. For example, if a new **treatment** only targets improvement of a **symptom** such as shortness of breath, other **symptoms** may not necessarily be impacted by that **treatment.** For this reason, it is essential that **concepts** to be used in a clinical trial are mapped to the **treatment** in development. Other **symptoms** important for patients should still be explored in the trial and it will be the decision of the clinical trial team/patient partners how this is addressed.

Overall, it is essential that patient partners, **sponsors,** and researchers work together during the COA measure selection stage. **Sponsors** and researchers may make invalid assumptions, that can be corrected by including patient partners during the COA measure selection phase.

Quote on COA measure

"The goal [of COA measure] should be to achieve a comprehensive evaluation of the patient expert/ partner experience most affected by the therapy, while maximizing the relevance of individual questions and minimizing overall burden and duplication." - Patient Expert

[29] Psychometric validation is beyond the scope of this module, for more information about validation of tools see FDA PRO guidance (2009) and Fayers and Machin – quality of Life third edition 2016.

[30] Please check the ISPOR webinar here and the Cosmin tool here.

4.1. What methods are commonly used for collecting patient partners' insights?

Community Advisory Boards/ Patient Advisory boards

Interviews/Focus Groups

Surveys/Questionnaires

Figure 10. Methods for collecting patient partners' insights in Step 4

4.2. Key questions of stakeholders engaged in the selection of COA measures

- How can this instrument make the most sense to the target patient population? Will this instrument help to reveal the critical issues for these patients?
- Does this make sense to patients? Does it cover their needs? Are the items / questions understandable?
- Will this instrument reveal all aspects of daily living for the patient and carers?

4.3. When does this step take place?

The research for the assessment of the suitability of the COA measure and COA measure selection should start as early as possible in the **treatment** development process and should be finalized before the start of a Phase 2 clinical trial. Ideally, a preliminary COA strategy (identification, implementation, interpretation, and communication of COA in the context of clinical trials) will be tested in Phase 2 and refined after Phase 2. The final COA strategy will be implemented in Phase 3.

Figure 11. Treatment development lifecycle and when the identification of relevant concepts takes place

Step 5
COA Adoption, Adaptation, and Development

Figure 12. Step 5 of the How-to Guide

If the evaluation done under Steps 3 and 4 reveals that no existing measure meets the selection criteria that are relevant to the **target population** and **context of use,** the adaptation of an existing measure or the development of a new measure should be considered. It should be noted, however, that the development of a new COA measure is a complex and time-consuming activity.

This is done in accordance with available guidelines[31] to meet the regulatory requirements. In addition, **sponsors** should communicate with regulatory authorities about their COA strategy and any feedback from regulatory authorities will need to be taken into account.

The work from steps 3 and 4 are required to inform the development of a new tool (for more info about developing a new COA measure, see **FDA guidance**[32]). The study team will develop draft COA questions based on the conceptual framework and discussions with patient partners and clinicians.

If patient partners are part of the study team, they can co-develop the wording of the item(s), before it is tested with a wider patient population. While the researchers need to ensure the questions measure exactly what they are supposed to measure, the patient team members can help in the comprehensibility and plausibility of the questions for the target patient population (**content** or **face validity**). In addition, patient partners' input can be valuable for identifying relevant recall periods, formatting of the tool, and mode of administration.

[31] Food and Drug Administration. (2020) Patient-Focused Drug Development: Collecting Comprehensive and Representative Input Guidance for Industry, Food and Drug Administration Staff, and Other Stakeholders. Available at: https://www.fda.gov/media/139088/download

[32] Food and Drug Administration. (2018) Patient-Focused Drug Development Guidance: Methods to Identify What is Important to Patients and Select, Develop or Modify Fit-for-Purpose Clinical Outcome Assessments. Meeting October 2018 Available at: https://www.fda.gov/drugs/news-events-human-drugs/patient-focused-drug-development-guidance-methods-identify-what-important-patients-and-select

Several validation approaches are applied in the testing phase, including the conduct of cognitive interviews with patients or the pilot testing of the **questionnaire** with the target patient population to demonstrate the **questionnaire** is content valid.

The confirmation of content **validity** (if not documented in the literature) and testing the tool with patient partners to ensure reliability are essential steps. They are also necessary if an existing COA measure is being adapted or a new one is developed.

Case example:

- With the clinical trial **sponsors'** assistance, a **Contract Research Organization (CRO)** approached three patient advocacy organizations, and each one referred several patients. The patients were consultants that reviewed and critically commented on a focus group interview guide.
- Each of the patient partners had variable quality-of-care experiences through their pathway. Their advice and stories affirmed the content of the focus group guide.
- Lessons learned and applied:
  - Avoid use of the word "journey" (i.e., cancer journey). A journey is something that is enjoyable and something for which one plans and anticipates. Cancer is not a journey and therefore the patients recommended using the terminology "care pathway".
  - The patients did not object to using the word "survivorship". They also did not object to using the word "palliative," but they did share that the term is often misunderstood as "end of life" and should be explained

5.1. What methods are commonly used for collecting patient partners' insights?

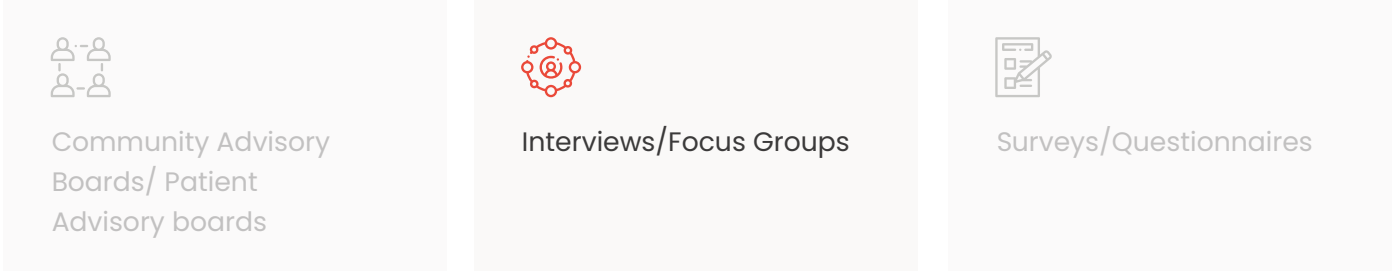

Figure 13. Methods for collecting patient partners' insights in Step 4

5.2. What specific information is provided?

The figure below outlines different types of criteria and questions that can be reviewed together with patient partners to assess the quality of a measure.

- Patient partners[33] should be involved during the entire development process to:
  - Provide disease-specific input, such as **signs/symptoms** of disease (e.g., frequency, severity, fluctuation, progression, chronicity, most bothersome, subpopulation differences, meaningful change); determine impacts of the disease on patients' lives and how they feel and function; and discuss the **treatment burden**;
  - Provide feedback (e.g., **via cognitive interviews**) on the draft version of the new COA measure (e.g. ensure the **items** and response options relevant and easy to understand, propose how the COA measure can be improved from the responders perspective).
  - Provide input on proposed response options or scoring and support the interpretation of the questionnaire, e.g., definition of **clinically meaningful** change (more detail in Step 7 on COA Data Interpretation).
  - Provide inputs on Patient, interviewer, or staff training and information (e.g., rationale for completing the COA measures, when/how these data will be used, etc.). Training is extremely useful to guarantee that all the participants complete the **questionnaire** in a standardized way across the study and that participants and staff understand the rationale for completing the **questionnaire** and how the data will be used to help address their needs and the needs of others with the same condition. Sufficient information needs to be given that patients and staff understand the implications or consequences of the COA data. This will help to limit bias such as social desirability (the tendency to give a favorable picture of oneself), acquiescence (the tendency to agree/disagree with statements regardless of logic or content), tendency to portray oneself in a negative fashion (e.g., with the hope of being assigned to the active treatment of the clinical trial versus to the placebo group) or experiencing anxiety in completing the **questionnaire**.

[33] In line with the Criteria of Representativeness of Stakeholders, it should include for example appropriate representativeness across various elements of diversity such as age, gender, race, socio-economic status, disease progression, geographic location, cultural differences, etc. See NHC, Tackling Representativeness at: https://nationalhealthcouncil.org/wp-content/uploads/2019/12/Representativeness%20in%20Patient%20Engagement.pdf

Case example[34]

Patient engagement in the elaboration and validation of a Psoriatic Arthritis Impact of Disease (PsAID) **score**

- Two patient experts represented the patients voice in a steering committee.
- Twelve patient research partners from different European countries participated in a work group. They supported the following activities:
  - Participated as equal partners with the other stakeholders (clinicians, nurses, researchers) in identifying domains, in formulating **items** for the **questionnaire,** in determining the number of **items,** the recall period and the **questionnaire** format.
  - Supported the translation of the **items** into different European languages.
- Patients participated in ranking and prioritizing the domains for importance (n=139) and were involved in cognitive debriefing interviews (n=65).

5.3. When does this step take place?

Given that both approaches - adaptation of an existing or development of a new COA measure - require much time, resources, and many level of engagement involving various stakeholders as well as comprehensive **psychometric** testing research, such efforts should start prior to Phase 2 in order to be able to implement the final version in the Phase 3 studies.

Figure 14. Treatment development lifecycle and when COA Adoption, Adaptation and Development takes place

[32] In line with the Criteria of Representativeness of Stakeholders, it should include for example appropriate representativeness across various elements of diversity such as age, gender, race, socio-economic status, disease progression, geographic location, cultural differences, etc. See NHC, Tackling Representativeness at: https://nationalhealthcouncil.org/wp-content/uploads/2019/12/Representativeness%20in%20Patient%20Engagement.pdf

[33] Wit M, Gossec L. Patients as Collaborative Partners in Clinical Research to Inform HTA. In: Facey KM, Ploug Hansen H, Single ANV, eds. Patient Involvement in Health Technology Assessment. Springer Singapore; 2017. doi:10.1007/978-981-10-4068-9

Step 6
COA Implementation within Clinical Trials[34]

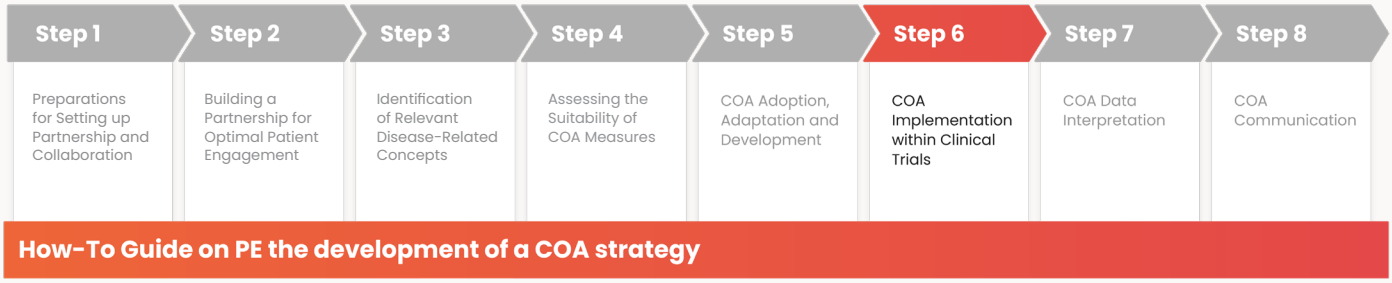

Figure 15. Step 6 of the How-to Guide

After the COA measure is identified and has been determined to be **fit-for-purpose,** it will be implemented in the clinical trial by being integrated into the clinical trial protocol (or study protocol). Patient partners play a critical role to review the clinical trial **protocol[35],** including (but not limited) to advise on:

1. The **COA endpoints,** i.e. position the COA as **primary, secondary** or further **endpoint** to meet the objective of the trial.
2. The feasibility for the trial participants to complete the COA as described in the **protocol,** i.e. define the order and timepoints of completion if more than one COA will be used and keep the number of measures to a minimum to try not to overburden patients.
3. The information provided to the clinical trial participants with regard to the rationale for completing the COA measure and how or when these data will be used.
4. The modality of the COA administration (e.g. some patients cannot complete written/paper measures but can type on a tablet).
5. Language and readability.

[34] Food and Drug Administration. (2019) Clinical Outcome Assessment Compendium. Available at: https://www.fda.gov/drugs/development-resources/clinical-outcome-assessment-compendium

[35] For more information check the How-to Guide on Patient Engagement in Clinical Trial Protocol Design: https://pemsuite.org/How-to-Guides/Patient-engagement-in-clinical-trial-protocol-design.pdf

6.1. What methods are commonly used for collecting patient partners' insights?

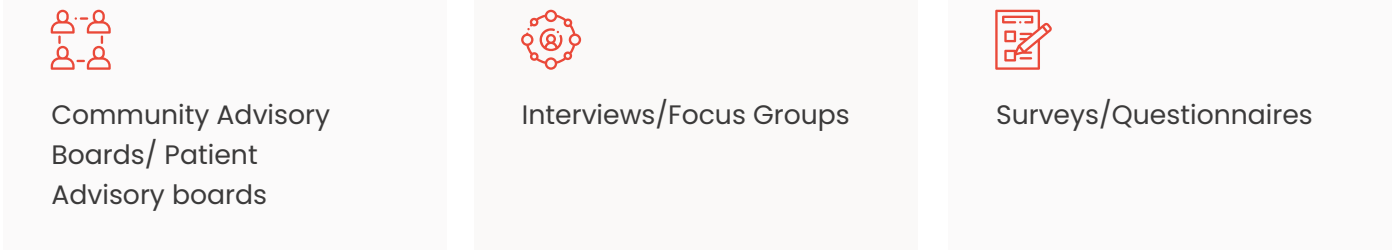

Figure 16. Methods for collecting patient partners' insights in Step 6

6.2. What specific information is provided?

Patient partners can provide recommendations on:

- **COA endpoint relevance:** are the COA endpoints meaningful and relevant?
- **Target clinical trial population:** does the COA research objective make sense as it relates to the specific patient population?
- **Feasibility for the clinical trial participants to complete the COA as described in the protocol[36], taking into consideration elements such as:**
  - Duration of the clinical trial
  - Target patient population characteristics: vulnerability of the populations (e.g., based on age, gender, health, treatment, ability to communicate effectively, mentally, visually, auditory and physically impaired patients, etc.), health literacy level, acceptability, expected levels of compliance, culture, language
  - Number of COA measures to complete, as wells as their frequency and order of completion
  - Length of COA measures, pictorial representations (e.g. for children), formatting
  - Method of administration (e.g., self-administration, interviewer-administration)
  - Mode and timing of administration (e.g., paper, electronic, phone)
    - Setting (e.g., home, clinic) to avoid bias, **placebo** effect, lack of privacy when completing the COA measures (e.g. in waiting room), and extent of flexibility in setting according to **patient preferences**
    - Assistance in filling out the COA measures (interview and filling out the answers, helping with the computer, reading out loud and defining words in the questions)
    - Mode of repeat-test (prefilled vs de-novo application)
  - Importance of literacy, e.g. being able to read/write.

As a guidance or checklist as to what COA information should be included in the clinical trial **protocol** and in the reporting, the SPIRIT (Calvert et al, 2018) consensus document may be useful. It describes 33 **items** that define the quality of a clinical trial **protocol** when a **patient reported outcome (PRO)** is a primary or key secondary outcome[37].

[36] For more information check the How-to Guide on Patient Engagement in Clinical Trial Protocol Design: https://pemsuite.org/How-to-Guides/Patient-engagement-in-clinical-trial-protocol-design.pdf

[37] Calvert M, Kyte D, Mercieca-Bebber R, et al. Guidelines for Inclusion of Patient-Reported Outcomes in Clinical Trial Protocols: The SPIRIT-PRO Extension. JAMA. 2018;319(5):483-494. doi:10.1001/jama.2017.21903

6.3. When does this step take place?

- During the clinical trial design and **protocol** development (i.e., before the start of the clinical trial; during phase 1 or Phase 2 of the clinical development) as well as during the design of the **informed consent form.**
- During the clinical trial or after completion of the clinical trial (i.e., during exit interviews or through a **survey**). In some cases, additional **questionnaires**/interviews during the clinical trial may be useful. However, any potential interference with the trial **protocol** or risk of influencing clinical trial participants should be minimized.
- Potentially, for issue management during the trial (e.g. recruitment or retention related, handling of patient questions or complaints).

Step 7
COA Data Interpretation

Figure 17. Step 7 of the How-to Guide

To be clinically relevant and supportive for clinical trial filing, a **COA endpoint** must be defined per **protocol** as a standalone **endpoint** among other **endpoints** to accurately measure the efficacy (and safety) of an intervention. Data analysis by statisticians helps to identify statistically significant changes observed with the new **treatment.**

However, small differences in COA score may be statistically significant yet not clinically meaningful and therefore, relying solely on a statistically significant change in the COA **score** (for example a difference between baseline and one month of treatment) to interpret the COA results is not sufficient. The concept of the **minimal clinically meaningful difference or meaningful within-patient change score (MW-PC)** has been proposed to define a threshold for meaningful change[38].

For example, the FDA specifies the requirement for defining the **clinically meaningful change** as follows: *"To aid in the interpretation of study results, FDA is interested in what constitutes a **meaningful within-patient change** (i.e., improvement and deterioration from the patients' perspective) in the **concepts** assessed by COAs."*[39]

There is extensive literature describing and appraising methods for defining minimally important differences and related terms and **concepts**[40]. **Anchor-based methods** and **distribution-based methods** are used to establish a threshold(s), or a range of thresholds, that would constitute a **MW-PC score** of the target COA for the target patient population.

While the **MW-PC** threshold is an important **concept** used in the interpretation of COA data, there is also some skepticism towards the attempt to define a single absolute threshold independent from target patient population, disease severity, or other factors, which may impact the perception of

[38] Hays RD, Woolley JM. The concept of clinically meaningful difference in health-related quality-of-life research. How meaningful is it? Pharmacoeconomics. 2000;18(5):419-423. doi:10.2165/00019053-200018050-00001

[39] Food and Drug Administration. (2019) Incorporating Clinical Outcome Assessments into Endpoints for Regulatory Decision-Making. Available at: https://www.fda.gov/media/132505/download

[40] Coon CD, Cook KF.Moving from significance to real-world meaning: methods for interpreting change in clinical outcome assessment scores. Qual Life Res. 2018;27(1):33-40. doi:10.1007/s11136-017-1616-3

meaningfulness[41].

Patient partners' insights are a valuable perspective on what constitutes **clinically meaningful change** for COAs. For example, during exit interviews, clinical trial participants are interviewed about perceived changes during the clinical trial and the value of those changes. It has been shown that the patient perspective on **clinically meaningful change** may differ from clinician assessments[42].

Patient partners may also provide additional input and context to support reimbursement discussions[43].

7.1. What methods are commonly used for collecting patient partners' insights?

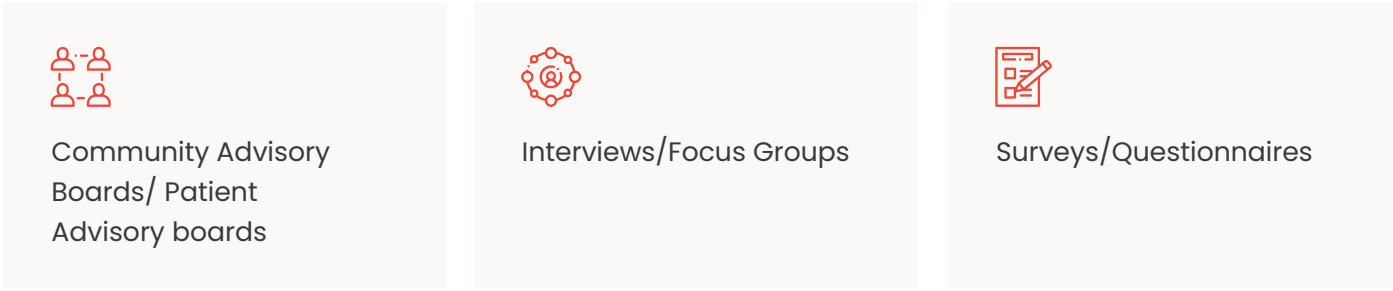

Figure 18. Methods for collecting patient partners' insights in Step 7

7.2. What specific information is provided?

- **Patient partners can:**
  - Provide comprehensive and representative input relating to disease, **treatment,** or meaningfulness of statistical analysis and results.
  - Provide input on the interview guide for purposes of the exit interviews; they will be asked to interpret findings from the patient perspective, and translate and communicate those findings with key stakeholders[44].

[41] 1. Hays RD, Woolley JM. The concept of clinically meaningful difference in health-related quality-of-life research. How meaningful is it? Pharmacoeconomics. 2000;18(5):419-423. doi:10.2165/00019053-200018050-00001

2. Weinfurt KP. Clarifying the Meaning of Clinically Meaningful Benefit in Clinical Research: Noticeable Change vs Valuable Change. JAMA. 2019;322(24):2381-2382. doi:10.1001/jama.2019.18496

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Gelhorn H, Kulke M, O'Dorisio T, et al. Patient-reported Symptom Experiences in Patients With Carcinoid Syndrome After Participation in a Study of Telotristat Etiprate: A Qualitative Interview Approach. Clin Ther.2016; 38 (4): 759-68.

Example

A patient expert with a diagnosis of Crohn's disease joined the research team at the start of a project that aimed to conduct interviews with individual patients. The patient expert reviewed the clinical trial documents and helped interpret the study findings.

7.3. When does this step take place?

The design of the exit interviews takes place during the development of the clinical trial protocol. The patient partners' input on the interpretation of the clinical trial findings takes place at the end of the trial.

Step 8
COA Communication

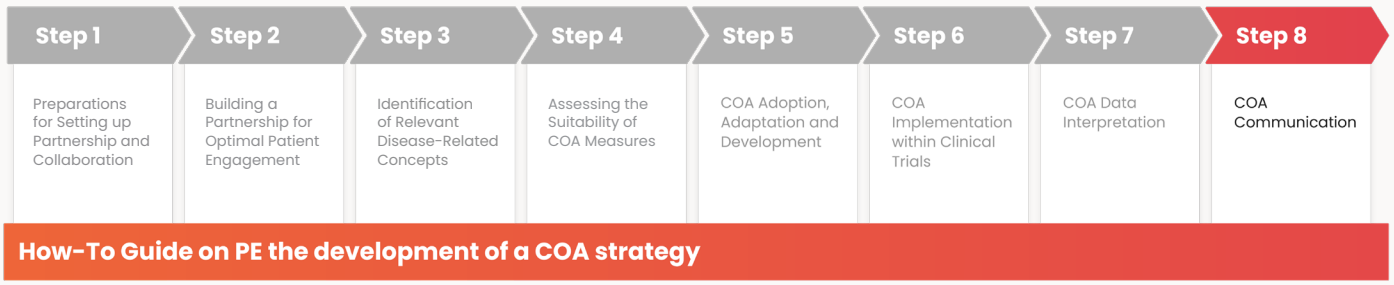

Figure 19. Step 8 of the How-to Guide

Communication of clinical trial results is generally done through product labelling, scientific communication and clinical trial reports[45]. Additionally, improving the clarity and meaningfulness of communications around COA data is critically important so that patients and physicians can understand and use the data collected in the clinical trials to inform their decisions.

The information provided through scientific communication is a key dissemination channel but is not always easily accessible to patients. The use of technical/scientific jargon in the communications, expensive subscriptions to journals and congresses registrations are several barriers that reduce patient access to published COA results. Moreover, a **Plain Language Summary** (PLS) may not often be developed for scientific publications, publications of interest to policy makers and congress sessions. However, as per EU regulation, a mandatory lay summary of the results of a clinical trial, including the COA data, should be made available as soon as possible.

Patient engagement can provide valuable insights to inform a publication and communication strategy and patient partners can participate as co-authors, can advise on communications channels, and support the co-development of effective **plain language summaries** to help overcome barriers to dissemination of COA results. For the latter aspect, a multi-stakeholder working group of PFMD has co-created a How-to Guide for patient engagement in plain language summaries (PLS)of publications and conference presentations[46] that can be consulted.

For sharing COA results with wider communities of patients through scientific communication channels (peer-reviewed journals and conferences communication) it is important to have a strategy that aims to ensure appropriate access and accessibility. In fact, it is important to consider different formats that are appropriate for the target patient population, such as audio or video formats.

A distinction should be made between patients that have been involved in the clinical trial and those patients that have not been involved in the trial but will use the data collected and published

[45] EFPIA EFGCP GLSP for clinical trials are considered

[46] More information available on the Plain language summaries (PLS)of peer-reviewed publications and conference presentations: practical 'How-To' Guide for multi-stakeholder co-creation at this link: https://pemsuite.org/How-to-Guides/WG5.pdf

to inform their decisions. For clinical trial participants, a robust communication/feedback process established upfront with the clinical trial sponsors will allow them to receive the results of the clinical trial once completed and become an active part of the dissemination to a wider patient public (e.g leveraging **plain language summaries** with using patient peer support groups and social media).

8.1. What methods are commonly used for collecting patient partners' insights?

Figure 20. Methods for collecting patient partners' insights in Step 8

8.2. What specific information is provided?

- **Patient partners:**
  - Co-develop with sponsors the clinical trial lay summary or **Plain Language Summaries** of peer-reviewed publications on COA.
  - Support dissemination of publicly available information on COA from the clinical trial.
  - Contribute as co-authors of publications and conference communications on COAs.
  - Advise on the wording for the treatment label.

8.3. When does this step take place?

Patient engagement for this step should take place alongside or shortly following the interpretation of COA results to be able to co-develop the communication strategy effectively.

COA communication and feedback typically take place at the end of a clinical trial once the data collected has been analyzed. It can also occur incrementally (e.g. an interim analysis) throughout a clinical trial, or collectively with the results of other similar studies.

Considerations for Quality Patient Engagement in the development of a COA strategy

The seven quality criteria of the Patient Engagement Quality Guidance (PEQG)[47] (see Annex 1 for definitions) can be considered in the different steps of Patient Engagement in COA strategy development. The guidance can be used from the planning phase through to the outcome of the project. These criteria have been adapted as practical considerations and applied where they fit best.

Figure 23. Patient Engagement Quality Criteria

Criteria 1 (Shared Purpose)

Considerations for Step 1, 2 and 3

Early involvement is a key factor for the quality of the patient engagement process and includes the integration of all perspectives in the early phases of project planning. Some key considerations include:

- Setting the foundation for a long-term, collaborative patient-sponsor relationship.

[47] For more information check https://pemsuite.org/peqg/

- Discussion on the aim of the project needs to take place with all stakeholders involved in the project (patients, sponsors, study team, clinicians…) at the very beginning of the project **(Criteria 1: Shared Purpose).**
- After the kick-off meeting, the agreed aims of the project will be widely communicated among the project stakeholders.
- Ensure to set and communicate clear expectations for patients and other project stakeholders. In particular, it is important that the patient partners involved understand the standard regulatory process and its limitations for onboarding new COA elements.

For patient partners it is important to be aware of:

- How long clinical research takes (for example, from the time the input is gathered, the use of existing COAs or the need for the development of a new COA and its inclusion in a research program).
- The technical complexity to be involved in COA projects

Criteria 2 (Respect and Accessibility)

Considerations for Step 3, 4 and 5

Criteria 2 Respect and accessibility for good patient engagement raise the importance of securing a supportive culture that reflects that all stakeholders acknowledge the patient perspective as equally important to that of other professional or authoritative stakeholders. Practical steps must be taken to ensure access for all. Considerations include:

- Quality time is scheduled on a regular basis with the stakeholders for discussions and feedback is provided throughout the entire project
- Patient partners have access to all information/documentation needed in suitable format and language (e.g. children and young people).
- All materials are sent prior to meetings or interactions.
- Translations of communications and materials should be considered if English is a barrier to understanding.
- Allow enough time for patient partners to go through material or complete surveys that are designed to be completed before in-person meetings.
- Meetings should be well planned, focused, and prioritized and not overwhelming & tiring. Individual patients and carers may be coping with multiple complex medical issues & appointments.
- Time and accessibility may need to be adjusted. Individual patients may experience brain-fog, visual impairment, fatigue and some might need additional support, extra time and materials in different formats and at an appropriate literacy level. If you don't know what the accessibility considerations are, contact a patient advocacy organization or consult directly with the individual to understand their needs.

Ensure that patient partners are compensated fairly for their contribution[48] and also have the possibility to decline to be compensated.

[45] For more information, review the resources co-created through the PFMD Patient Engagement Remuneration & Fair Market Value project: https://pemsuite.org/fmv/ and the Patient Engagement Compensation and Contracting Toolbox developed for use in the USA by the National Health Council.

Criteria 3 (Representativeness of Stakeholders)

Considerations for Step 4, 5 and 6

Consider diversity for a target patient population group **(Criteria 3: Representativeness of stakeholders)** and the efforts to balance representation should always be made and documented.

It is demanding but essential for any patient engagement activity and involves careful consideration of the selection of patient representatives.

For example, patient partners from a particular country or region may have different experiences in healthcare than others due to several factors. A mixture would be ideal, such as a **Patient Advisory Board** that include different patient profiles.

Example

- In focus groups or patient interviews, use sampling quotas (e.g., age, gender, ethnicity, culture and country , availability of standard of care, etc.) to represent the population of the condition under consideration.
- If relevant, involve younger populations, elderly, carers, and traditionally underrepresented populations.
- Consider cultural differences and familiarity with devices as they may differ by regions/ countries/ generations.

Criteria 4 (Roles and Responsibilities)

Considerations for Step 2, 3, 4 and 6

Clarification of roles and responsibilities **(criteria 4)** of all stakeholders is essential for the implementation of equitable working practices that ensure opinions and expertise are respected and incorporated where possible into Patient Engagement projects. Helpful practices include:

- Documentation and agreement of the roles and responsibilities of all the stakeholders involved in the project should be outlined before Step 3, but also during the different phases of the project as roles may evolve.
- Development of contingency plans if stakeholders can no longer be involved in the project.

Criteria 5 (Capacity & Capability)

Considerations across all steps 1 - 8

Ensure stakeholders have relevant knowledge to contribute adequately to the COA project. Wilson et al. (2017) recommend to "ensure that diverse perspectives are captured, training may be provided to individuals with less acumen and knowledge of scientific methods."; This can be done by setting clear expectations at the start of a project. Resources and time are also important considerations to ensure genuine engagement.

- Interview/screen stakeholders to ensure key criteria are met to fully engage in the project. Identify appropriate roles based on stakeholder capacity and capability. Where there are limitations in capabilities provide resources or training.
- All stakeholders involved in the project should receive the requested support education and training **(Criteria 5 Capacity & Capability):**
  - **Patients** can receive training on the aspects of COA strategy and COA measures that will be relevant to the project.
  - **Patient organizations** can help their communities on the relevance of COAs. The level of education/training proposed should adapt to the type of activities in which the patient partner is engaged.
  - **Clinical trial teams and sponsors** should receive training on how to involve patient partners in the development of a COA strategy in each of the steps described in the How-to Guide.

Criteria 6 (Transparency in communication and documentation)

Considerations for steps 3, 4, 5, 6, 7 and 8

Transparent communications in a clear and balanced way is critical in all steps of a patient engagement project. Throughout the process, you may want to consider:

- Establish bi-directional communication among all stakeholders, providing opportunities to share, respond, agree, and disagree to any project-related questions at selected stages of the project.
- Develop a communication plan prior to the project and regular communication between stakeholders.
- Ensure patient partners can identify and raise issues and collaboratively design solutions.
- Confidentiality agreements may be necessary to ensure protection of data shared among stakeholders.
- Collect feedback periodicallypost sessions to ensure communications areit is accessible and manageable.

Criteria 7 (Continuity and Sustainability)

Considerations across all steps 1 - 8

Projects should progress smoothly and can be planned to ensure continuity of the project and relationships from beginning to end. Efforts to maintain ongoing relationships after a project concludes can also extend collaboration beyond a single project. Some considerations for continuity and sustainability include:

- Conduct alignment meetings and regular project updates to ensure all stakeholders are informed and remain engaged. Meetings can be virtual or physical depending on the feasibility.
- Ensure that work is evenly distributed and stakeholders remain engaged throughout the process.
- Set ground rules for feedback from both sides for a commitment to continuous improvement.
- Explore if there are opportunities to share learnings beyond this project, can there be a broader application of this project or its outcomes?

Acknowledgements

This How-to guide was co-developed with a large community of stakeholders (more than 30 individuals from 26 organizations), representing patient organizations, pharmaceutical industry, academics, researchers, and external experts.

Special thanks to the Core team for drafting, editing, reviewing, and maintaining momentum to deliver the guide, present it on multiple occasions and disseminate it even further than their own internal networks. We would like to also acknowledge all contributors* of this working group and everyone who reviewed the multiple iterations of this guide during 2019 and 2020. Your contribution made a difference and resulted in the How-to Guide in your hands today.

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Annex 1
Patient Engagement Quality criteria definitions

The Patient Engagement Quality Guidance (PEQG[46]) was co-created to help all stakeholders set up partnerships and projects collaboratively.

Criteria 1 : Shared purpose

This refers to the project's aims and outcomes that all stakeholders taking part should agree on before starting the project. Consider putting in place processes to help facilitate discussions between all stakeholders to identify each other's values, expectations, and objectives, and review and discuss priorities in the planning of the project. It can be valuable to enable stakeholders to exchange views openly to understand the scope and objectives of the project, acknowledging that some of their objectives may differ. All parties concerned should also have a shared written description of the common goals of the project.

Criteria 2: Respect and accessibility

This refers to (1) respecting each other, and respectful interactions within the project to be established among partners, and (2) openness to and inclusion of individuals and communities (to the project) without discrimination. Considerations to ensure good conditions to implement the project should be made from the beginning. For example:

- simplification of wording
- budget and payment considerations
- cultural adaptations to procedures
- practicalities such as meeting timing, location and format
- accessibility of project materials
- written co-developed rules of conduct

Accessibility to participate may be facilitated by enabling multiple ways to involve stakeholders who could benefit from and/ or contribute to the project. For example, patients with cognitive impairment might need more time to go through project material, or need printed versions rather than electronic documents or PDFs for easier reading.

[46] PFMD. (2018) Patient Engagement Quality Guidance Tool. Patient Focused Medicines Development. Available at: https://pemsuite.org/peqg/

Criteria 3: Representativeness of stakeholders

This refers to the mix of people you involve, which should reflect the needs of the project, and the interests of those who may benefit from project outputs (for example, target population). Consider diversity in expertise, experience, demographics, and other relevant criteria for inclusion. When selecting Patient Engagement stakeholders, patients, attention will be given to awareness of the diversity required to achieve visible representative voice.

Criteria 4: Roles and responsibilities

This refers to the need for clearly agreed, and ideally co-created roles and responsibilities, in writing, addressing that all aspects of project needs will be established upfront and revisited regularly

Criteria 5 : Capacity and capability for engagement

This refers to (1) capacity as having relevant and dedicated resources from all stakeholders (for example, providing a dedicated point of contact by the sponsor and having allocated sufficient time by all stakeholders to allow genuine engagement); and (2) capabilities for all stakeholders to enable meaningful engagement (for example, the level of knowledge, expertise and training stakeholders might need to deliver Patient Engagement activities throughout the project). Consider supporting stakeholders to build the required capacity and capabilities for this project in different forms of training both with sponsor organizations and with each stakeholder (for example, helping to understand the context, processes, relevant terminology etc.). Both capacity and capability building are intended to facilitate participation and lower barriers to collaborate.

Stakeholders can be given access to learning resources and given dedicated support (if needed).

Capability needs may vary depending on the project needs, but also e.g. personal circumstances of Patient Engagement representatives.

Criteria 6: Transparency in communication and documentation

This refers to the establishment of communications plan and ongoing project documentation that can be shared with stakeholders. Communication among stakeholders must be open, honest and complete. In addition, adequate up-to-date documentation must facilitate communication with all stakeholders throughout the project. Consider proactively and openly sharing progress updates throughout the project externally. In addition, communicating outcomes of the project to all stakeholders and how their contribution was of value to the success of the project is critical.

Criteria 7: Continuity and sustainability

This refers to the smooth progression of the project, as well as efforts to maintain ongoing relationships with stakeholders. Consideration should be given for the role of stakeholders beyond a single project. When starting the project, consider including in your project plan the actions needed for maintaining expected flow of the project from beginning to end. Create a plan to nurture relationships with your partners and stakeholders involved during the project, and when needed and requested, beyond the project as well. For all stakeholders successful planning and personal and organizational resilience should be anticipated.

Annex 2
Resources and tools to consider

National Health Council, Clinical Outcome Assessment (COA) series

Description:

The series will continue to introduce COA-related topics, but also will cover a broader range of subjects, including patient preference research, patient engagement in clinical trial design, as well as medical device development.

It is built on the belief that: understanding patient experiences, goals, and needs leads to: clinical trials that are more efficient and measure outcomes patients really care about; more commercially successful medicines because potential barriers to uptake were identified and addressed earlier; and health technology/value assessment that evaluate drugs based on patient-defined value. Please have access to the webinars here.

ISPOR, Patient-Centered Research Webinar series[47]

Description:

To advocate for a meaningful use of PROs to best reflect patient reality, patient advocates need to understand what PROs are, how PROs are being measured, and how they can bring the patient perspective into development, use and reporting of PRO measurements. This information will be presented across a 3-part webinar series:

- Patient-Reported Outcomes Webinar 1 (3-Part Series): Webinar 1: What are PROs and HRQOL Tools?
- Patient-Reported Outcomes Webinar 2 (3 Part Series): Generating PRO Data – and Using It
- Patient Reported Outcomes Webinar 3: Developing New Patient-Reported Outcomes Instruments.

Please have access to the webinars here, and select the webinar of interest.

EUPATI, Patient- Reported Outcomes assessment

Please have access to the resource here.

https://www.isoqol.org/category/webinar/webinar-series/

ISOQOL, Adapting PROs for Research and Clinical Practice Series[48]

- Methods for modifying PRO measures for clinical practice and clinical research use. Please access here.
- Methods for incorporating CATs (including ePROs) into clinical trials and clinical practice – operational and scientific challenges and solutions. Please access here.

[47] Registration required.

[48] Registration and fee payment required.

Glossary of terms

This glossary represents the words used in this How-to Guide and intends to provide more clarification or explanation to the terminology used. The explanations should by no means be taken as the sole meaning as context might influence the understanding of these terms. The list at the end references the resources that were used to create this glossary.

Terminology	Explanation
A	
Anchor-based methods	Used as external criteria to define patients who have experienced a meaningful change in their condition. The meaningful change scores of the COA measure can then be derived from the group of patients who are identified as having experienced meaningful change based on the anchor measure(s). Sponsors should provide evidence for what constitutes a meaningful change on the anchor scale (Source: FDA, PFDD Public Workshop Guidance, 2019)
C	
Carer	Persons supporting individual patients such as family members as well as paid or volunteer helpers (IMI PARADIGM, PE Toolbox: Glossary, 2020).
Clinically meaningful change	To aid in the interpretation of study results, FDA is interested in what constitutes a meaningful within-patient change (i.e., improvement and deterioration from the patients 'perspective) in the concepts assessed by COAs) (FDA, 2019)
Clinical Outcome Assessments (COA)	Assessment of a clinical outcome can be made through a report by a clinician, a patient, a non-clinician observer, or through a performance-based assessment. Types of COAs include patient-reported outcome, clinician-reported outcome measures, observer-reported outcome, and performance outcome. (Source: BEST (Biomarkers, EndpointS, and other Tools) Resource, 2016)
COA Clinical Endpoint	Clinical endpoints are distinct measurements or analyses of disease characteristics observed in a study or a clinical trial that reflect the effect of a therapeutic intervention (Principles of Translational Science in Medicine (Second Edition), 2015)
Clinician-Reported Outcomes (ClinRO) measures	A measurement based on a report that comes from a trained health-care professional after observation of a patient's health condition. Most ClinRO measures involve a clinical judgment or interpretation of the observable signs, behaviors, or other manifestations related to a disease or condition. ClinRO measures cannot directly assess symptoms that are known only to the patient (e.g., pain intensity). (Source: BEST (Biomarkers, EndpointS, and other Tools) Resource)

Terminology	Explanation
C	
Concept (also referred to as Concept of Interest)	In a regulatory context, the concept is the aspect of an individual's clinical, biological, physical, psychological, social or functional state, or experience that the assessment is intended to capture (or reflect) (Source: BEST (Biomarkers, EndpointS, and other Tools) Resource).
Concept elicitation (interviews):	A process or method to collect a holistic set of relevant concepts (i.e., disease and treatment symptoms and associated impacts) that are important to patients from relevant stakeholders (e.g., patients, experts, caregivers) (FDA, 2019).
Context of use	The term context of use refers to the comprehensive descriptions that fully and clearly delineate the setting, manner, and purpose of use of the ClinRO assessment. When used in clinical trials for development of medical interventions, context of use includes specifying how the ClinRO assessment is intended for use as an endpoint in clinical trials. As stated previously, ClinRO assessments are not in and of themselves end points (Patrick et al., 2017).
Contract Research Organization (CRO)	A person or an organization (commercial, academic, or other) contracted by the sponsor to perform one or more of a sponsor's trial-related duties and functions (Source: EMA, 2017).
D	
Disease Burden (also referred to as burden of disease):	The impacts, direct and indirect, of the patient's health condition that have a negative effect on his or her health, functioning, and overall well-being. Disease burden includes but is not limited to the physical and physiologic impacts of the disease and its symptoms; comorbidities; emotional and psychological effects of the disease, its management, or its prognosis; social impacts; effects on relationships; impacts on the patient's ability to care for self and others; time and financial impacts of the disease and its management; and considerations of the impacts on the patient's family (Source: FDA, 2020).
Distribution-based methods:	They can be used to categorize changes as small, moderate, and large and often can be combined with anchor-based estimates to provide confidence in the responder definition. Distribution-based methods for determining clinical significance of particular score changes should be considered as supportive and are not appropriate as the sole basis for determining a responder definition (FDA, 2009).
E	
Endpoint	The measurement that will be statistically compared among treatment groups to assess the effect of treatment and that corresponds with the clinical trial's objectives, design, and data analysis. For example, a treatment may be tested to decrease the intensity of symptom Z. In this case, the endpoint is the change from baseline to time T in a score that represents the concept of symptom Z intensity (FDA, 2009).

Terminology	Explanation
F	
Fit-for-Purpose:	A conclusion that the level of validation associated with a tool is sufficient to support its context of use (Source: BEST (Biomarkers, EndpointS and other Tools) Resource).
G	
Health-related quality of life (HRQL)	Health-Related Quality of Life considers many different aspects related to a person's perception of quality of life affected by health status. These include physical, psychological, functional, and social aspects (Source:EUPATI, Toolbox: Glossary).
Health Technology Assessment bodies	A body that undertakes or commissions health technology assessment to form recommendations or advice for healthcare funders and decision-maker on the use of health technologies (PARADIGM, 2020)
I	
Informed consent form (ICF)	A document that describes the rights of a study participant and provides details about the study, such as its purpose, duration, required procedures, and key contacts. Risks and potential benefits are explained in the informed consent document. (Source: NHI, NIA Glossary of Clinical Research Terms)
Instrument	A means to capture data (i.e., a questionnaire, diary) plus all the information and documentation that supports its use. Generally, that includes clearly defined methods and instructions for administration or responding, a standard format for data collection, and well documented methods for scoring, analysis, and interpretation of results in the target patient population (FDA, 2009).
Item	An individual question, statement, or task (and its standardized response options) that is evaluated by the patient to address a particular concept (FDA, 2009).
M	
Meaningful Within-Patient Change (MW-PC)	To holistically determine what is a meaningful change, both benefit and risk, improvement and deterioration, may need to be accounted for. As such, special consideration should be given by the sponsor to assess how meaningful the observed differences are likely to be. To aid in the interpretation of the COA-based endpoint results, sponsors should propose an appropriate threshold(s) (e.g., a range of score change) that would constitute a clinically meaningful within-patient change in scores in the target patient population for FDA review.
Measure	Synonym of instrument.

Terminology	Explanation
O	
Observer-reported Outcome (ObsRO)	A measurement based on an observation by someone other than the patient or a health professional such as a parent, or other non-clinical caregiver who regularly observes the patient in daily life and is in a position to report on a specific aspect of the patient's health. This type of measure or observer report is without medical judgment or interpretation, and includes events or behaviours that can be observed in patients who cannot communicate themselves (e.g. infants or cognitively impaired) (Source: EUPATI, Toolbox: Glossary).
P	
Patient Advisory Board (PAB)	Also called Community Advisory Board (CAB) refers to a group of patients who offer their expertise to sponsors of clinical research and who advise several sponsors in their field. CABs are autonomous bodies, not related to the sponsor or chosen by them (IMI PARADIGM, 2020)
Patient Experience Data (PED)	Patient experience data can be interpreted as information that captures patients' experiences, perspectives, needs, and priorities related to: 1. the symptoms of their condition and its natural history; 2. the impact of the conditions on their functioning and quality of life; 3. their experience with treatments; 4. input on which outcomes are important to them; 5. their preferences for outcomes and treatments; and 6. the relative importance of any issue as defined by patients. (FDA, 2020)
Patient partner	A patient that partners with sponsors in the development of a COA strategy, the term can include: • Individual patients: Persons with individual experience of living with the disease or pre-identified presenting risk factors. Technical knowledge in research, development and regulatory is not required as the main role is to contribute with their subjective experience on the disease, diagnostics and treatment. • Carers: Persons supporting individual patients such as family members, paid or volunteer helpers. • Patient advocates: Persons who have insight and experience in supporting a larger population of patients living with a disease. They contribute with the experience acquired personally and form the group which they represent. • Patient experts: Persons with individual experience in the disease and additional technical knowledge in medicines R&D and regulatory affairs through training or experience. • Patient organization representatives: Persons who are mandated to represent and express the collective views of a patient organization on a specific issue or disease area. These individuals may or may not be patients or carers themselves. (IMI PARADIGM, PE Toolbox: Glossary, 2020)

Terminology	Explanation
P	
Patient Organizations	Not-for-profit legal organizations (including the umbrella organizations that it belongs to) mainly composed of patients and/or carers. They provide support to patients and advice to clinical research teams (IMI PARADIGM, PE Toolbox: Glossary, 2020).
Patient Preference	A statement of the relative desirability or acceptability to patients of specified alternatives or choice among outcomes or other attributes that differ among alternative health interventions (Source: FDA, 2020).
Patient-reported outcome (PRO)	A measurement based on a report that comes directly from the patient (i.e., study subject) about the status of a patient's health condition without interpretation of the patient's response by a clinician or anyone else. A PRO can be measured by self-report or by interview, provided that the interviewer records only the patient's response. Symptoms or other unobservable concepts known only to the patient (e.g., pain severity or nausea) can only be measured by PRO measures. PROs can also assess the patient perspective on functioning or activities that may also be observable by others. (Source: "BEST (Biomarkers, EndpointS, and other Tools) Resource")
Performance Outcome (PerfO) measures	A type of clinical outcome assessment. A measurement based on a standardized task(s) performed by a patient that is administered and evaluated by an appropriately trained individual or is independently completed. PerfOs require patient cooperation and motivation. These include measures of gait speed (e.g., timed 25-foot walk test), memory recall (e.g., word recall test) or other cognitive testing (e.g., digit symbol substitution test). (Source: BEST (Biomarkers, EndpointS, and other Tools) Resource)
Placebo	An inactive pill. This is sometimes called a "sugar pill". In some studies, participants may be assigned to take a placebo rather than the study medication. (Source: FDA, 2019)
Plain Language Summary	A non-technical summary of clinical trial results or other content in a journal article or congress presentation. This How-To guide refers to PLS for publications and conferences and do not include PLSs that are created per EU regulations (ie, layperson summaries) that follow a certain regulatory rigor (Source: EMA, 2017)
Primary endpoints	The main result that is measured at the end of a study to see if a given treatment worked (e.g., the number of deaths or the difference in survival between the treatment group and the control group). What the primary endpoint will be is decided before the study begins (Source: EMA, 2010).
Protocol	A document that describes the objectives(s), design, methodology, statistical considerations, and organization of a trial. The protocol usually also gives the background and rationale for the trial, but these could be provided in other protocol referenced documents. A protocol amendment is a written description of a change(s) to or a formal change of a protocol (Source: NHI, NIA Glossary of Clinical Research Terms).

Terminology	Explanation
Q	
Qualitative Research Methods	Methods associated with the gathering, analysis, interpretation, and presentation of narrative information (e.g., spoken or written accounts of experiences, observations, and events). Qualitative research methods may also include direct observations (e.g., nonverbal communication and behaviors) (Source: FDA, 2020).
Quality of life	A general concept that implies an evaluation of the effect of all aspects of life on general well-being. Because this term implies the evaluation of non-health-related aspects of life, and because the term generally is accepted to mean what the patient thinks it is, it is too general and undefined to be considered appropriate for a medical product claim.
Quantitative research methods	Methods associated with the gathering, analysis, interpretation, and presentation of narrative information (e.g., spoken or written accounts of experiences, observations, and events). Qualitative research methods may also include direct observations (e.g., non-verbal communication and behaviors) (FDA, 2020).
Question-naire	A set of questions or items shown to a respondent to get answers for research purposes. Types of questionnaires include diaries and event logs (FDA, 2009).
R	
Regulatory bodies	Also referred as regulatory authority (or regulatory agency or in short 'regulators'): A body that carries out regulatory activities relating to medicines, including the processing of marketing authorisations, the monitoring of side effects, inspections, quality testing and monitoring the use of medicines (IMI PARADIGM, 2020)
Risks	Risks are adverse events and other unfavorable effects associated with a medical product. Risks include drug interactions, risks identified in the non-clinical data, risks to those other than the patient (e.g., fetus, those preparing and administering the medical product), and risks based on pharmacologic class or current knowledge of the product. Factors such as potential misuse, abuse, or diversion of the product may also be considered (Source: FDA, 2020).
S	
Score	A number derived from a patient's response to items in a questionnaire. A score is computed based on a prespecified, validated scoring algorithm and is subsequently used in statistical analyses of clinical trial results. Scores can be computed for individual items, domains, or concepts, or as a summary of items, domains, or concepts (FDA, 2009).
Secondary endpoint	Results that are measured at the end of a study, in addition to the main result (primary endpoint) to see if a given treatment worked. Secondary endpoints can explore other aspects of the treatment (Source: EMA, 2010).
Sign	Any objective evidence of a disease, health condition, or treatment-related effect. Signs are usually observed and interpreted by the clinician but may be noticed and reported by the patient (FDA, 2009).

Terminology	Explanation
S	
Side effect	An unintended response to a medication. Side effects, or adverse reactions, are generally regarded as being harmful, and may occur after a single dose or prolonged administration. They might result from the normal use of a medicine or from the use of a medicine in a way unintended by the marketing authorization holder (MAH) – such as taking an overdose or from the combination of two or more medicines being taken at once. (Source: EUPATI, Toolbox: Glossary)
Sponsor	An individual, company, institution, or organization that takes responsibility for the initiation, management, and/or financing of a clinical trial.
Surveys	This is a relatively closed format when patients answer a number of predefined questions and have limited opportunity to bring up their own points (or do not have such opportunity at all, depending on the design of a survey). Surveys are relatively low in effort and cost and are used when the drug development team intends to receive feedback regarding specific concern(s) they have with regards to protocol design or explore perceptions of a particular topic. Online ones - there may be GDPR requirements to do.
Symptom	Any subjective evidence of a disease, health condition, or treatment-related effect that can be noticed and known only by the patient.
T	
Target population	Also referred to as target patient population, underlying population, or intended population. The group of individuals (patients) about whom one wishes to make an inference (FDA, 2009).
Treatment	Throughout this How-to Guide, the term treatment will refer to drugs, as well as to medical technologies.
Treatment Burden	(also referred to as burden of treatment) The impacts of a specific treatment or treatment regimen that have a negative effect on the patient's health, functioning, or overall well-being. Treatment burden includes: side effects, discomfort, uncertainty about treatment outcomes, dosing and route of administration, requirements, and financial impacts (FDA, 2009).
Treatment benefit	The effect of treatment on how a patient survives, feels, or functions. Treatment benefit can be demonstrated by either an effectiveness or safety advantage. For example, the treatment effect may be measured as an improvement or delay in the development of symptoms or as a reduction or delay in treatment-related toxicity. Measures that do not directly capture the treatment effect on how a patient survives, feels, or functions are surrogate measures of treatment benefit (FDA, 2009).
V	
Validity	Validity refers to the degree to which an outcome measure measures the construct it purports to measure, and contains the measurement properties content validity (including face validity), construct validity (including structural validity, hypotheses testing, and cross-cultural validity\measurement invariance) and criterion validity.

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