How-To Guides for Patient Engagement

PATIENT FOCUSED MEDICINES DEVELOPMENT

How-to Guide on Patient Engagement in Clinical Trial Protocol Design

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 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 drug development continuum. Each How-to Guide functions as a standalone tool but can also be easily combined with the other How-to 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;
- Plain language summaries (PLS) of peer-reviewed publications and conference presentations: practical 'How-To' Guide for multi-stakeholder co-creation.

How was it developed?

The Guide is a true example of co-creation, having involved more than 35 multi-stakeholders contributors from more than 26 organizations, including patient experts, the pharmaceutical industry, clinical research organizations, and external consultants with the relevant experience/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) is proposed as a reference in planning and preparing for involving patients in the process of designing a clinical trial protocol. The seven Criteria of the PEQG have been specially adapted to fit the scenarios, type of activities and stakeholders involved.

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

[2] Please find the Patient Engagement Quality Guidance resources here: https://pemsuite.org/peqg/. The Patient Engagement Quality Guidance can support the preparation and planning of a partnership in the process of Clinical Trial Protocol Design. 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.

Who is this guide for?

This How-to Guide has been developed for anyone who needs to be involved in the implementation of Patient Engagement in the design of a clinical trial protocol. Specifically, this Guide has been co-created to:

- Allow for comprehensive guidance to be outlined in a single document.
- Compile information related to specific steps in the patient engagement process in sequential sections, even if information is repeated, in order to eliminate the need to consult multiple documents.

The guide will give more clarity, instructions and the key terminology to Patients, Carers, Patient Organizations, Industry (Pharma, Biotech, Devices), Academia, Researchers, Contract Research Organisations (CROs) on how to co-create a clinical trial protocol with patients.

In the guide, the use of the terminology of "Sponsor" makes reference to a person, company, academic institution or other organization that initiates, manages (including collecting and analyzing the data) or finances a clinical trial.

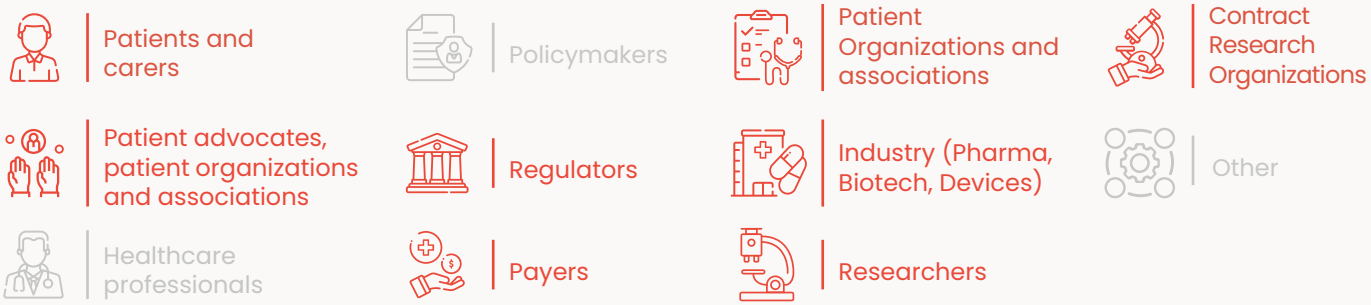

Figure 1. Relevant stakeholders in patient engagement in the clinical trial protocol design

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 4 steps that outline key moments and aspects for patient engagement in clinical trial protocol design, including:

- **Step 1 - Preparations for setting up partnership and collaboration**
  This step focuses on the definition of collaboration goals to prepare for a meaningful partnership. This also includes the identification and selection of the partnership activities.
- **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 engagement activities. It also considers other stakeholders that can be involved to understand patients' perspectives and drive successful outcomes from patient engagement.
- **Step 3 -Patient Engagement in the Clinical Trial Protocol Design**
  This step focuses on ensuring that the protocol is co-developed with patient partners in order to take into account the practicalities, logistics, unmet needs, safety, ethics, and data collection that add value and adequately capture meaningful endpoints and patient outcome.
- **Step 4 -Feedback and follow-up**
  This step focuses on providing guidance on ways to continue the collaboration after the formal ending of the initial project.

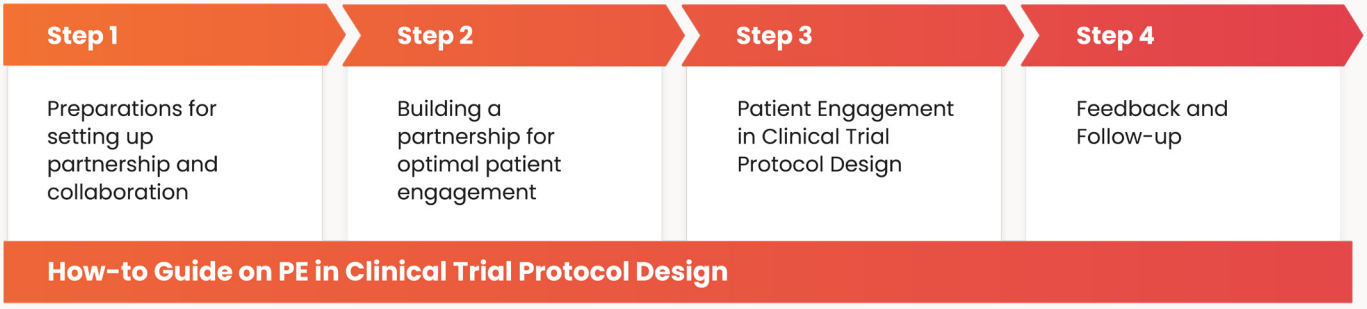

Figure 2. How-to Guide on PE in Clinical Trial Protocol Design

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

Context

A successful clinical trial is a key milestone of the medicine development continuum. There is strong evidence that a well designed clinical trial **protocol** can not only impact patient recruitment but also help overcome retention issues. Patients' continued involvement throughout a clinical trial can also lead to an increase in use and uptake of research results by other patients and the healthcare system as a whole[4]. Patient engagement in clinical trial protocol design ensures that a clinical trial is designed to consider the patient's perspective.

A well-designed protocol takes into account the unmet needs, safety, ethics, and data collection that add value and adequately capture meaningful **endpoints** and patient outcomes[5] but also the practicalities and logistics aspects. In addition, it is gathering information to strengthen study designs and optimize clinical trial procedures & execution, clinical **endpoints**, and data generation so that they are seen as valuable to and address the needs and preferences of the patients, while also being supportive for subsequent regulatory and reimbursement discussions if applicable.

The role of **patient partners**[6] helping the sponsors with the co-design of the clinical trial protocol is becoming recognized as a good practice to establish systematically. However, little is known on **how** to proceed with the engagement of patient partners, and **when** the partnership should be initiated to generate the highest impact.

This How-to Guide builds on existing guidelines (PCORI, Transcelerate, CTTI) and provides directions for meaningful patient engagement throughout the process of the development of the clinical trial protocol.

[4] Patient-Centered Outcomes Research Institute (PCORI). (2018) The value of Engagement. Available at: pcori.org/engagement/value-engagement

[5] For more information, check the How-to Guide on Patient Engagement in the Development of a Clinical Outcome Assessment (COA) strategy. Available at: link available when How-to Guide will be finalized.

[6] Which differ from the clinical trial participants.

Step 1
Preparations for setting up partnership and collaboration

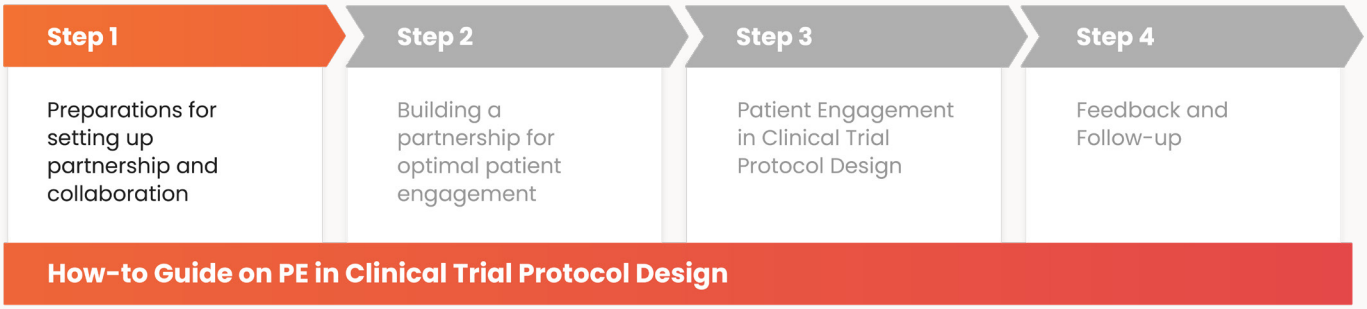

Figure 3. Step 1 of the How-to Guide

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

- **Define partnership and collaboration goals** to prepare for meaningful, effective and respectful interactions and 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 patients' 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 on which they wish to seek input from patients. A patient organization may be looking for opportunities for their 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 patient partners and initiate a partnership

Identify patient partners

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

Brief considerations 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 size, scope, and geographical footprint of their network?
- Other capabilities and competencies needed from the patient partner[7].

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 the right match for the right activity.

The patient organization and sponsors should also consider:

- Does their infrastructure allow them 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[8].

[7] Access at: http://imi-paradigm.eu/PEtoolbox/pe-capabilities/. See also "Tackling Representativeness" from the National Health Council. Add footnote: NCH "Tackling Representativeness" Available at: https://nationalhealthcouncil.org/wp-content/uploads/2019/12/Representativeness%20in%20Patient%20Engagement.pdf

[8] 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

Initiating a partnership

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 partnership in research, apply the general principle of 'as early as possible'. Ideally, establish contacts a year before embarking on the design of the clinical trial protocol, 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[9].

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.

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[10].

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.

[9] 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/

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

Four levels of contribution, each increasing in complexity:

1. Patients can provide **insights into the disease burden**, the patient pathway, patient needs and preferences for clinical trials/research methodology;
2. Patients can provide **generic insights** such as assessing if the clinical visit schedule is too heavy and whether there could be transportation issues;
3. Patients can provide input on **study design**, including inclusion/exclusion criteria and endpoints; are familiar with the design of a clinical trial protocol and can co-create patient interview guides and plain-language summaries for clinical trial participants;
4. Patients have vocational backgrounds relevant to medicines development.

Step 2
Building a partnership for optimal patient engagement

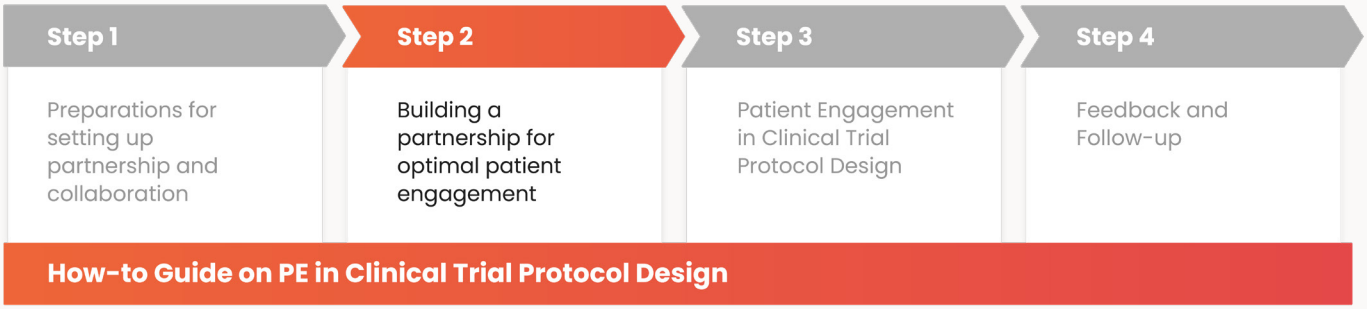

Figure 4. Step 2 of the How-to Guide

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 driving 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 patients' perspective and preparing patients for an optimal project kick-off.

Building a partnership between patients and sponsors will help build the trust that is critical to successful collaborations in medicines 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[11] or the National Health Council's Rubric for Good Patient Engagement as practical tools to guide preparation and interactions when project planning with patient partners.

In setting up a project plan and goals, partners should address the following:

- Use of the Patient Engagement Quality Guidance[12] 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 clinical trial protocols and their design.

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

- What impact will 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 experience 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 drug 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.

[12] 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

[13] 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 clinical trial protocol design.

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[13] and anxiety experienced during this phase can be alleviated by an honest and straightforward conversation about the process and potential difficulties.

[13] 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:

- 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
- Principles for Contracting between Patients/Patient Groups and Pharmaceutical Companies for Patient Engagement Activities, 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?	
If no, Connect with the legal , compliance, data privacy teams to enquire about the time requirement to set up contracts and relay this information to patient partners	
» What is the time requirement 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, refer to the National Health Council's Patient Engagement Compensation and Contracting Toolbox[14] and the Guiding Principles on Legal Agreements.[15])	
» 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 patients, carers, and patient organizations 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 medicine or health care solution, may not happen. It is equally important that sponsors are aware that engaging patient partners requires proper resources and time input.

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

[15] 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

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, development of a protocol design and patient partner inclusion in a **clinical development** program.
- Establish an understanding of where the clinical trial protocol fits into the overall development of a product, and how patients can have an impact.
  - Even if the clinical trial does not progress to the next clinical stage, patients 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 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[16]

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.

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 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.

[16] 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/

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-design and co-development of the clinical trial protocol. Stakeholders can serve on ad hoc working groups to prioritize unanswered research questions, co-develop and review the clinical trial protocol. 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 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[17].

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 design a clinical trial protocol 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 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 of a clinical trial protocol in development.

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

Example of engagement type[18]	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.

Figure 5. Example of engagement types

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 clinical trial protocol design 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, epidemiologists, statisticians, legal and compliance teams.

- **Clinical research teams:** This includes relevant individuals in the sponsor organization that are working on the clinical development program or clinical trial. It is important to consider if the clinical research team understands and recognizes the benefits of incorporating the learning

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

from patient engagement, as well as how to incorporate patient insights into the 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 clinical trial protocol development responsibility, 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 for the final.

Step 3
Patient Engagement in the Clinical Trial Protocol Design

Step 3 focuses on the importance of reflecting patient partners' input together with the sponsor in the design of a clinical trial protocol through co-creation principles. A clinical trial protocol is 'a document that describes the objective(s), design, methodology, statistical considerations, and organization of a [clinical] trial. The protocol usually also gives the background and rationale for the trial.[19]

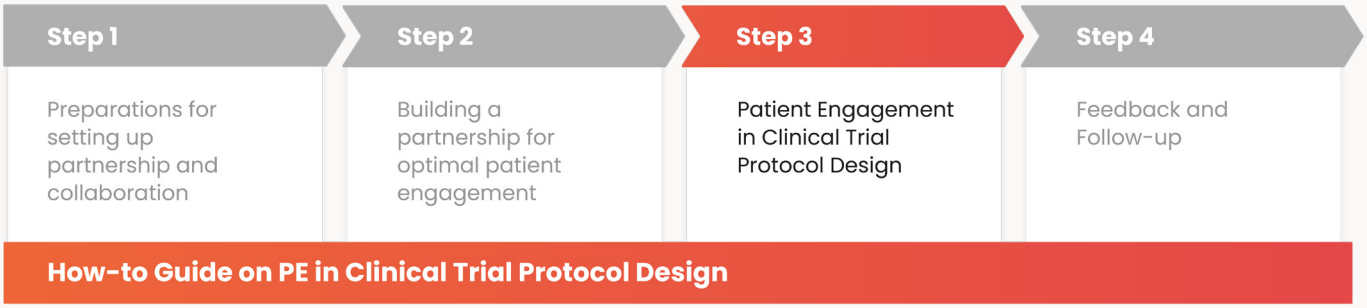

Figure 6. Step 3 of the How-to Guide

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

- **Gather information to strengthen study designs** and optimize clinical trial procedures and execution, clinical endpoints, and data generation.
- **Ensure** that the target populations see these as valuable and that they **address their needs and preferences** while also supporting subsequent regulatory and reimbursement discussions (if applicable). A well-designed **protocol** is co-developed with patient partners and takes into account the practicalities, logistics, unmet needs, safety, ethics, and data collection that add value and adequately capture meaningful **endpoints** and patient outcomes.[20]

3.1. Collecting patient partners insights for Clinical Trial Protocol Design

Collecting patient partners' insights via the **most appropriate methods**[21] is crucial. Some sponsors may have no previous experience in working with patient partners. Involving patient partners with varying degrees of exposure to/involvement in clinical trials protocol development is important for gaining a diversity of perspectives that will help improve the clinical trial design. Also, involving patient

[19] National Institute of Health (NIH). (n/a) NIA Glossary of Clinical Research Terms. Available at: https://www.nia.nih.gov/research/dgcg/nia-glossary-clinical-research-terms

[20] For more information, check the How-to Guide on Patient Engagement in the Development of a Clinical Outcome Assessment (COA) strategy: link available when How-to Guide will be finalized.

[21] For additional information on the methods for collecting patients' insights please check the section Deciding on the formats for sponsor–patient partner interaction

partners who have never taken part in a clinical trial before can be insightful. Current approaches for collecting patient feedback may vary; however, 'translating' those insights back to the study sponsor and research team can still be challenging.

To fully integrate patient insights into the protocol design, attention is needed on how those insights are communicated so they can be actioned for a patient-centric trial design. The barriers sponsors face in collecting patient insights need to be overcome for this information to have a meaningful impact on the protocol and overall study design.

This includes not only support from the internal organization but also an understanding of timelines and any need for additional research to identify practical methods that support how patient insights on the protocol can have a positive impact on the trial across all stakeholders.

Such methods are increasingly being used to support other healthcare decision making, including predicting patient update of treatments.[22]

For Sponsors and Patient Partners

The following considerations specific to clinical trial participants should be discussed with the patient partners involved in the clinical trial protocol design to ensure it is implemented optimally:

- Are we addressing an unmet need with this research?
- Are the inclusion and exclusion criteria appropriate? Are we excluding certain populations, for safety, for instance?
- Have we included **Patient Reported Outcome Measures**? If so, are they appropriately timed and/or appropriately chosen?
- Are there any geographic, cultural, age, gender, race, language, socio-economic status specific considerations that we need to address when we identify participants for the clinical trial?
- Have we considered all possible clinical trial sites, or can we consider new sites? Depending on the scope of the study (international, regional, country-specific), the specific considerations may be tailored and adapted with the support of the patient partners.
- Are there specific considerations that may impact the clinical trial participants (e.g., drug packaging or the use of (unfamiliar) devices for administration)?
- Are there specific considerations that may impact a clinical trial participants' life (e.g., frequent travel to hospital, hospital stays, privacy impacts)?
- Will the clinical trial include any invasive procedures? Could these have a negative affect on willingness to participate?
- Are there special considerations where children or vulnerable populations are involved?
- Is the therapeutic area one that may provoke sensitivities?
- If the study participants will be using a new digital tool (e.g., smartwatch, tablet, smartphone, etc.), are there practical implications (e.g., is training needed)?

[22] Soekhai, V. et al, (2018) Discrete Choice Experiments in Health Economics: Past, Present and Future. PharmacoEconomics, 37, (201–226). Available at: https://link.springer.com/article/10.1007/s40273-018-0734-2

- Could timing/volume of procedures in a clinical study have negative practical implications for clinical trial participants or disrupt their quality of life? If so, can the schedule and/or operational set-up of the clinical trial be redesigned to address this[23]?
- Will there be lay language materials (e.g., brochures, booklets, videos, etc.) to help clinical trial participants understand the clinical trial and the Informed Consent documents?
- Will the sponsor implement electronic Informed Consent for the clinical trial (e.g., eConsent or ePRO) and are there any special considerations needed?
- Is there a clear commitment from the sponsor to sharie the study results in an understandable format (leaflets, brochures, ad hoc communication at conferences) and in plain language?
- How will the sponsor share study progress in terms of enrollment of clinical trial participants, active clinical trial sites, and timelines?

Additional considerations

Planning and assuring a timely outcome so the findings collected from patient partners can be embedded before the protocol is finalized. In this planning phase, linking in parallel to the collection of site feedback would be useful.

Managing expectations: As clinical trial protocols are based on templates aligned with legal and regulatory requirements, there will be some aspects that cannot be changed significantly based on the input from the patient partners. To manage expectations, sponsors should be transparent about these instances from the outset and as part of the feedback and follow-up.

Manage conflicts of interest: Patient partners providing input in the clinical trial design might also be interested in and eligible to take part in that clinical trial later on. Consider how to avoid any potential conflicts of interest around this from the outset (e.g., by keeping patient partners anonymous or communicating with patient partners indirectly via a patient organization).

3.2 Key questions and considerations for the development of a clinical trial protocol with patient partners

Patient partners can be engaged to develop a clinical trial protocol from the start, or they may be asked to review a clinical trial protocol that has already been drafted. In either case, the sponsor will need to ensure that the patient partner understands the context of the **clinical development** plans relevant to the clinical trial at hand.

Patient engagement in clinical trial protocol design should allow for insights to be implemented; therefore, early engagement with patient partners and outlining the timelines are critical. **Table 1** outlines the typical sections of a clinical trial protocol, adapted from a standard template[24].

[23] Please find more resources in the TransCelerate Patient Protocol Engagement Toolkit. Available at: https://www.transceleratebiopharmainc.com/ppet/planning-for-patient-engagement/

[24] NIH-FDA. Clinical Trial Protocol Template v0.1 20160205. Available at: https://osp.od.nih.gov/wp-content/uploads/2014/01/Protocol_Template_05Feb2016_508.pdf

It provides a series of questions and considerations relevant to each section of the clinical trial protocol that can be discussed and designed with **patient partners**.

This table does not provide an exhaustive list of all aspects to be addressed in designing the clinical trial protocol; however, it does provide a starting point for sponsors and patient partners to help take patient engagement into account in clinical trial protocol design.

Clinical trial protocol section	What is addressed in the section of the protocol?	Questions and considerations that are relevant to clinical trial participants and/or aspects where patient partners can provide protocol advice
Objectives and purpose	This section of the protocol provides a detailed description of the primary (and secondary) objectives of the study. The objective is based on the scientific questions to be answered and the reason for performing the clinical trial.	• Why is there a need for the study? What, if any, is the current standard of treatment? • Do the study objectives address an area of unmet need? • What is important to the patient in the treatment/ maintenance of their condition? • What would a patient (or carer) hope to get out of study participation? • Is it a novel treatment? • What would the patient like to see a drug/device bring to them to make living with their disease easier? • What is meaningful for the patient for treatment/ maintenance of their condition?
Study design and endpoints	The design of the study (e.g., type of study, phase, single, **multicenter** or decentralized) and the study **primary, secondary** (and exploratory) **endpoint(s)** should be drawn up based on the study objective(s).	Overall Study Design • Is the study design appropriate? • Is there a need for a 'study partner' (carer or family member)? If so, is their role and responsibility during visits explained clearly? • What changes to the design could be implemented to minimize the burden on the patient participant? Investigational product/placebo/standard care • Does the clinical trial have a **placebo**? Does the trial have different randomization strata? If so, what considerations are needed for explaining these to the clinical trial participant? • Is the use of the comparator treatment or **placebo** justified? • Assuming this is a **blinded clinical trial**, it is Important that patients do not unintentionally unblind it. Sharing study-specific information on social media is probably not advisable.

Clinical trial protocol section	What is addressed in the section of the protocol?	Questions and considerations that are relevant to clinical trial participants and/or aspects where patient partners can provide protocol advice
Study design and endpoints		Study Endpoints • Is the study endpoint meaningful to the patient population? • Which study outcomes are most important to the patient? Do the primary/secondary endpoints in the protocol map to this? • How important are patient-relevant endpoints? Are the current measurement approaches appropriate? Or is there a lack of patient-relevant endpoints? • What patient-reported outcomes or other patient experience measures are appropriate? • Are the patient-reported measures captured in a practical way (i.e. on paper, tablet, etc.)? • Will any study endpoints be related to patient-reported outcomes data? Additional measures • Are there requirements in the study that may add additional burden? (e.g., colon prep agents)
Study enrollment and withdrawal	This section of the protocol encompasses the study population, the **inclusion and exclusion criteria,** and the recruitment and retention approaches of the study, and how participants may withdraw or be discontinued from the study.	Inclusion/Exclusion criteria • Is the study population appropriate (also in terms of diversity: gender, age, sex, ethnicity)? • Do the inclusion/exclusion criteria present a barrier to recruitment? Patient Screening/Recruitment • Are the patient-facing documents, such as recruitment materials and **Informed Consent Forms (ICF)**, clearly written and understandable for patients? • Are the benefits and risks clarified in the **ICF**? If not, have the potential benefits and risks of participation been identified for the patient? And for their caregivers? • Are support services offered during the screening process? • What happens if, following screening, a potential clinical trial participant is not eligible?

Clinical trial protocol section	What is addressed in the section of the protocol?	Questions and considerations that are relevant to clinical trial participants and/or aspects where patient partners can provide protocol advice
Study enrollment and withdrawal	This section of the protocol encompasses the study population, the **inclusion and exclusion criteria,** and the recruitment and retention approaches of the study, and how participants may withdraw or be discontinued from the study.	• What kind of support services would be helpful when participating in the clinical study? • What type of information would patients like to receive as part of a clinical trial, and from whom? (e.g., peer, doctor, patient organization, family member) • What value does the patient see from the clinical trial for them and other patients with the condition? • Is there a recruitment strategy and recruitment tools for patients, sites, clinics? Participant withdrawal • Are the procedures for withdrawing from the study clearly communicated? • How will patients be appropriately followed up if they discontinue the study? Patient Remuneration • Are any clinical trial participation costs reimbursed? And are their other financial or non-financial incentives for participation (e.g., vouchers, medical or technological devices, etc.)? • How will the burden on the clinical trial participant and carers be alleviated (e.g., clinical assessment and travel, meals, accommodation reimbursement, child care, if applicable)? Management of care • How will the study impact the patients' current care? • What are the other conditions of participation? • When will the study begin, and how long will it last? After the trial • What are the procedures when a clinical trial participant needs to leave the study (e.g., withdrawal or termination), and how will they be followed-up? • What will happen from the clinical trial participants perspective when the study ends? • Will the study drug be provided after the trial? If so, for how long? Is there an added cost or how? • What happens to the patient data during the study or when the clinical trial is completed/discontinued?

Clinical trial protocol section	What is addressed in the section of the protocol?	Questions and considerations that are relevant to clinical trial participants and/or aspects where patient partners can provide protocol advice
Study enrollment and withdrawal		Other • What study assurance is needed in case of medical problems due to the study? Are the risks mentioned and explained to the study participants? • What are the barriers and motivators to participating in a particular study?
Study agent (if applicable)	The study agent is the intervention being studied (e.g., drug, device). The dosing and administration schedule should be described (e.g., dose, time of day and interval, route of administration) and should include conditions for dose adjustments/modifications/ delays and the duration of the therapy.	Dosing • What is the daily dose? • How might participants feel about dose escalations or scheduling changes? • How will possible dose adjustments/delays affect the patient? Mode of Administration • How will the study agent be delivered? (e.g., oral, intravenous, etc.) • Are there practical considerations around the administration (e.g., length of visits, suitable formulation for study population)? Treatment duration • What is the expected duration of treatment? Other relevant questions • How does the treatment differ from the current (if any) standard of treatment? • Is there a process for patients to ask questions about the agent? • Are any new technologies being used in the study? And are there related practical considerations?
Study procedures and schedule (if applicable)	Procedures and scheduling for the collection of data (medical history, height, weight, BMI , sex, age, demographic group, health status of participants), including clinical, laboratory and imaging results, and questionnaires, should be defined.	• What does taking part mean to the patients ('What's going to happen to me and what impact will it have on my life?')? • Is the schedule of events feasible in terms of screening, enrollment/baseline, and follow-ups? • Is the visit schedule feasible (e.g., frequency of visits, length of visits, at-home requirements)?

Clinical trial protocol section	What is addressed in the section of the protocol?	Questions and considerations that are relevant to clinical trial participants and/or aspects where patient partners can provide protocol advice
Study procedures and schedule (if applicable)		• What does taking part mean to the patients ('What's going to happen to me and what impact will it have on my life?')? • Is the schedule of events feasible in terms of screening, enrollment/baseline, and follow-ups? • Is the visit schedule feasible (e.g., frequency of visits, length of visits, at-home requirements)? • Is the order of the tests and procedures during visits realistic for patients (e.g., urine testing isn't the first test if people have a long distance to drive to the site or have a bladder control issue and cannot hold it for their travel distance)? • Are the tests and procedures included needed to answer the study objectives? Or are they more 'exploratory' in nature? • Is the frequency of the tests and procedures realistic? (e.g., minimize the number of lumbar punctures, propose optional sub-groups for specific tests and procedures) • Are the geographical locations and number of sites enrolling participants appropriate? • What are the considerations when choosing study sites, testing, accessibility, and diversity of the patient population? • How many questionnaires will participants need to complete at each visit? • How and when will patients receive their test results? • Would alternatives to study visits (nurse home visits or telemedicine) would improve patient participation? • How long are patients willing to spend on answering questionnaires (e.g., are there multiple PROMs/ questionnaires each visit)? • Does the patient need to attend the clinic, or can they complete the questionnaires at home? • How are you going to gather patient feedback, specifically on **patient-reported outcome questionnaires** (e.g., clarity of language, comprehension, appropriateness of questions

Clinical trial protocol section	What is addressed in the section of the protocol?	Questions and considerations that are relevant to clinical trial participants and/or aspects where patient partners can provide protocol advice
Study procedures and schedule (if applicable)		asked) and on devices used (e.g., whether the use of a hand-held device is easy or difficult)? • Is there a questionnaire for the caregiver? (if yes, the same questions as above would be applicable)
Assessment of safety	This section of the protocol outlines the assessments and procedures related to risks and safety, and the steps that will be taken to ensure the safety of clinical trial participants and minimize risk.	• What information is provided to clinical trial participants to help them understand possible **side effects?** • How will **adverse events** be classified and reported? • Are there any risks to individuals other than the clinical trial participants (e.g., carers or close contacts)? • Is the process for reporting **side effects** clear for patients? • How will the patient contact the study coordinator throughout the study with concerns, worries, or **side effects**, including during evenings and at weekends?
Ethics	Clinical trials of human participants must conform to ethical standards. This section of the protocol outlines the ethical considerations, including, among many considerations, information on the **Informed Consent** procedures and participant and data confidentiality.	• What are the Informed Consent procedures? • Are there supplemental materials available to help clinical trial participants (and carers) understand the study and the Informed Consent Form(s)? • What considerations are needed around Informed Consent or assent in paediatrics or those who cannot consent for themselves? • Will any of the data or samples collected in the clinical trial be used elsewhere? • Will an independent review board approve the study protocol?
Data handling and recording keeping	This section of the protocol outlines the data handling and record-keeping for the clinical trial, including study records retention.	• Who is responsible for the collection and management of the clinical trial participants' data? For how long will it be retained? • Will clinical trial participants be able to request their data at a later date? • Are the personal data used in accordance with GDPR (in Europe)?

3.3 Analysis of patient partner insights

The analysis of patient partner insights will serve the adaptation/amendment of the clinical trial protocol before the start of the clinical trial **recruitment**. Patient partners' inputs are essential in determining what is important and the importance of specific aspects for the patient population, which are often then analyzed qualitatively.

In addition to sharing their insights, **patient partners** can play an integral role in developing the operational plan as a research partner. Refining the clinical trial design based on patient partner input means the research will cover aspects valued by the patient population. Doing so will likely have a positive effect on **recruitment** speed and retention of clinical trial participants.

Good practices for Sponsors:

- Create a 'knowledge library' of patient partners' insights, with their consent, so learnings are shared more broadly and can inform work on future clinical trials.
- Summarize storage of patient insights for regulatory filing.
- Communicate with patient partners throughout the study duration; this may include sharing press releases, clinical trial updates and published data, including any reasons for study discontinuation.
- Inform patient partners if their input to a single clinical trial protocol is applied to other related clinical trials or clinical development programs.

Step 4
Feedback and follow-up

Step 4 encompasses reasons for the sponsor to stay in touch with patient partners. It is an important step for the future of patient-centric clinical trials. Maintaining the relationship beyond the project enhances the likelihood of future collaborations and increases the efficiency of patient engagement activities, which will help increase their impact.

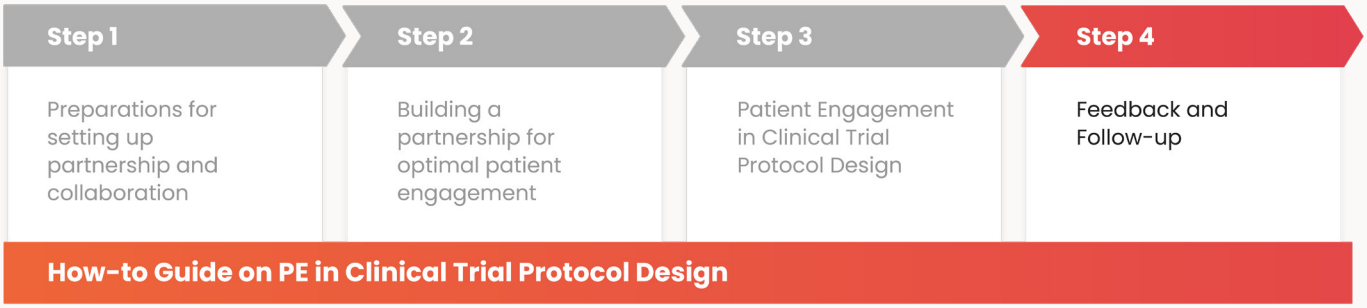

Figure 7. Step 4 of the How-to Guide

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

- **Provide guidance on ways to continue the collaboration** after the formal ending of the initial project. The sponsor and patient partners should be considered equal partners with meaningful follow-up emphasizing the value placed on the inputs and relationship. Furthermore, an ethical rationale goes with involving and informing the populations that are providing feedback.

Once the clinical trial protocol has been completed, sponsors should share information with patient partners on the specific areas where inputs were incorporated and how they influenced the clinical trial protocol or other study elements.

The sponsor should equally explain to patient partners, as appropriate, why certain insights could not be incorporated. Sponsors should also be clear about timelines for the clinical trial and when they expect it to be complete and the results published.

Patient partners can continue to be engaged and informed once a clinical trial is underway. Examples of continued engagement and information sharing can include:

- Informing the patient partners on the progress of the clinical trial, including recruitment, completion and/or publications

- Asking patient partners to contribute to the **Plain Language Summary**[25] of the clinical trial
- Including patient partners in the process of manuscript/abstract writing and/or review.

Advantages of long-term patient engagement

There are many advantages to keeping the sponsor–patient partners collaboration going. The sponsor can reflect on past projects and support **patient partners** to disseminate clinical trial outcomes to the wider community, highlighting how their contribution made a difference to the outcomes. Opportunities to circulate results via publications or conferences should be shared with the contributing patient partners as they can help to get the right messages to the relevant patient communities.

Plan with the patient partners how best to keep in contact after the project. See whether a debrief is possible/practical after a certain period of time or specific milestones are achieved to reflect on and assess the impact of the collaboration. This would also be an ideal opportunity to gauge how far-reaching the benefits of the partnership have been and should be outlined in the contract created at the beginning of the partnership.

[25] 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

Considerations for Patient Engagement

Below you can find Considerations for quality PE for each step of this How-to Guide on PE in Clinical Trial Protocol Design. Access the Annex 1 for more considerations on the PEQG and definitions of the 7 criteria. The Patient Engagement Quality Guidance (PEQG) tool[26] provides a useful discussion guide and partnership-setting framework to help set up the new partnership and keep it on track.

Figure 8. The PEQG tool has 7 quality criteria

Considerations for Step 1:
Preparations for setting up partnership and collaboration

In the preparation of the partnership between patients and sponsors it can be valuable to enable stakeholders to exchange views openly, in order to understand the scope and objectives of the future collaborations, 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 (**Criterion 1: Shared Purpose).**

[26] Find here more information on the Patient Engagement Quality Guidance tool.

Considerations for Step 2:

Building a partnership for optimal patient engagement

During this phase, roles and responsibilities should be acknowledged by all parties (**Criterion 4: Roles and Responsibilities**), described in a written format, addressing that all aspects of the project need to be revisited regularly. Capacity for engagement (**Criterion 5: Capacity and Capabilities for engagement**) refers to the critical point of having the relevant and dedicated resources from all stakeholders.

This includes for example foreseeing and defining a main point of contact for the patients involved in the projects for the entire duration of the established partnership. It also entails having realistically estimated and communicated the patient partners' time availability for a qualitative contribution. In the context of design of the partnership for the clinical protocol design, developing the capabilities for all stakeholders (**Criterion 5**) to enable meaningful engagement is critical.

In fact, the success of the PE partnership is based on a sufficient level of knowledge, access to the right expertise, and training resources (e.g. material and dedicated support functions) for all stakeholders (patients and sponsors). Capability requirements may vary depending on the project nature and complexity, and should be clearly addressed. It requires a strong assessment process during the establishment of the partnership.

Considerations for Step 3:

PE in Clinical Trial Protocol design

During the collection of patients' insights, the good conditions to allow openness to and inclusion of individuals and communities without discrimination is critical (**Criterion 2: Respect and accessibility**).

Make sure that people involved are reflecting the needs and limitations of the patient population when developing the clinical protocol, and the interests of those who may benefit from being enrolled in the clinical trial. Consider diversity in demographics, cultural, health conditions and other relevant criteria for inclusion.

When selecting patient partners, attention will be given to awareness of the diversity and expertise required to achieve a visible representative voice and provide tangible positive benefits on the future design of the protocol. It is recommended to have one accountable person from the sponsor for patient interactions. While there will be several people interacting, there should be one delegate, who has the overview and central accountability (**Criterion 3: Representativeness of Stakeholders**).

A transparent and open communication process must be established at the beginning of the collaboration with the patient partners and will continue throughout the entire lifecycle of clinical trial included in the steps of data results collection, dissemination and external communication.

Transparent means to include changes to study design, outcomes, rationale for choices, etc. Confidentiality agreement needed to protect information shared by both parties, sponsor and patient (**Criterion 6: Transparency in Communication and Documentation**).

Considerations for Step 4:
Feedback and Follow-up

The follow-up actions regarding the analysis of the insights need a proactive communication process with the patient partners that must be open, honest and complete.

For any insights collected from the patient partners that cannot be taken into consideration in the development of the protocol there is a need to install a systematic feedback mechanism with clear explanations provided by the sponsor (**Criterion 6: Transparency in Communication and Documentation**). When possible, the relationships between the patient partners involved and sponsors of the clinical trial will continue beyond the project (**Criterion 7: Continuity and sustainability**) to create the basis of a long-term partnership.

Acknowledgements

This How-to guide was co-developed with a large community of stakeholders (more than 35 individuals from 26 organizations), representing patient organizations, pharmaceutical industry, academics, researchers and external experts.

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Annex 1
Patient Engagement Quality criteria definitions

The Patient Engagement Quality Guidance (PEQG[27]) 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.

[27] 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 a communication 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.

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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	
Adverse effects/events	Any untoward or unfavorable medical occurrence in a clinical research study participant, including any abnormal sign (e.g. abnormal physical exam or laboratory finding), symptom or disease, temporarily associated with the participants' involvement in the research, whether or not considered related to participation in the research. (Source: NIH, NIA Glossary of Clinical Research Terms)
B	
Blinded clinical trial	Blinding is a procedure in which one or more parties in a trial are kept unaware of which treatment arms participants have been assigned to, in other words, which treatment was received. (EUPATI, The concept of blinding in clinical trials)
C	
Clinical development	Clinical development is one step in the process of bringing new medicines or treatments to the market. They follow different phases designated as Phase I, II, III (and IV after marketing authorization). (Source: EUPATI, Toolbox: Glossary)
Clinical Trial Participants	Individuals that participate in a clinical trial.
Compassionate use	Expanded access, also called "compassionate use", provides a pathway for patients to gain access to investigational drugs, biologics and medical devices for serious diseases or conditions. Investigational drugs and devices have not yet been approved by the regulatory bodies, e.g., the US Food and Drug Administration, and they have not been proven to be safe and effective. Therefore, they may be effective in the treatment of a condition, or they may not. It is important to remember that the drug/biologic/medical device may have unexpected serious side effects and that patients need to consider all the possible risks when seeking access to an investigational medical product (Source: FDA, 2019).
Control group	The group of participants that receives standard treatment or a placebo. The control group may also be made up of healthy volunteers. Researchers compare results from the control group with results from the experimental group to find and learn from any differences (Source: FDA, 2019).

Terminology	Explanation
C	
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).
E	
Endpoint	Principal indicator(s) used for assessing the primary question (i.e., hypothesis) of a clinical trial. A variable that pertains to the efficacy or safety evaluations of a trial. An endpoint is more specific as compared to an outcome since it relates to the planned objective of the study (Source: FDA, n/a).
Ethics committee	An independent body made up of a range of individuals including medical or scientific professionals and non-medical or non-scientific members (e.g., patients or lay members). An ethics committee may operate within an institution, or it may be national, or supranational or private. Ethics committees have a responsibility to ensure the protection of the rights, safety and wellbeing of research participants, as well as assuring the public of that protection. It operates, among other things, expressing an opinion on the clinical trial protocol, the suitability of the investigators involved in the trial, the adequacy of facilities, and on the methods and documents to be used to inform trial participants and obtain their informed consent. A trial should only begin when a favorable opinion by an ethics committee has been given. Ethics committees may also monitor studies once they have begun and after they are complete. (Source: EUPATI Toolbox: Glossary)
Exclusion criteria	Characteristics that exclude people from taking part in a trial. For example, depending on the requirements of the trial, exclusion criteria might include age, sex, type or stage of disease, and the presence or absence of other medical conditions. Exclusion criteria (and inclusion criteria) are an important part of a trial protocol. If they are properly defined, exclusion and inclusion criteria will increase the chances of a trial producing reliable results. They also protect participants from harm and help avoid exploitation of vulnerable people (such as those unable to provide informed consent). The reasons for choosing the exclusion criteria should be documented with the trial protocol. Exclusion of certain groups can affect how realistic it is to generalize the trial results to the relevant patient population (external validity). This should be considered by researchers when they are designing a trial, and unnecessary exclusions should be avoided. (Source: EUPATI, Toolbox: Glossary)
I	
Inclusion criteria	Characteristics that potential participants must have in order to be considered for participation in a trial. They describe the patient population and patient selection criteria. Inclusion criteria should specify the type of testing used to make the patients' diagnoses, as well as specific disease requirements (for example, how severe the disease is, failure or success with previous treatments, plus any other factors that might affect prognosis such as age, sex, or ethnicity). The inclusion criteria (and exclusion criteria) are important parts of a trial protocol. If they are properly defined, inclusion and exclusion criteria will increase the chances that the trial produces reliable results. They also protect participants from harm and minimize the risks. (Source: EUPATI, Toolbox: Glossary)

Terminology	Explanation
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: NIH, NIA Glossary of Clinical Research Terms)
M	
Multicenter Trial	A clinical trial that is carried out at more than one medical institution. (Source: NIH, NCI Glossary of Cancer Terms)
P	
Patient	• **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 from the group 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 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. • **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. • **Patient partners:** patients that partner with the sponsor and are actively involved in the development of the clinical trial protocol.
Patient-reported outcome (PRO)	Measures of the subjective experience or view of a participant in a clinical study. It is not a clinical measure, or an assessment made by anyone else involved in the study. PROs are commonly collected by asking patients to fill in questionnaires, or by interviewing patients. Questionnaires or interview guides used as part of clinical studies should undergo extensive testing to ensure they are reliable and valid. PROs can be used to assess, for example, symptoms as experienced by the patient, e.g., disability, quality of life and other health perceptions. There are many published PRO questionnaires dealing with aspects of quality of life. Some have been developed for specific conditions or treatments. Some are designed to be general, such as the 'EuroQoL' or 'EQ-5D', which has been translated into many languages and is used extensively in clinical trials. (Source: EUPATI, Toolbox: Glossary)
Placebo	An inactive substance or other intervention that looks the same as, and is given the same way as, an active drug or treatment being tested. The effects of the active drug or other intervention are compared to the effects of the placebo. (NCI Dictionary of Cancer Terms)

Terminology	Explanation
P	
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 does not include PLSs that are created per EU regulations (e.g., 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. (NCI Dictionary of Cancer Terms)
Protocol	A detailed plan of a scientific or medical experiment, treatment, or procedure. In clinical trials, it states what the study will do, how it will be done, and why it is being done. It explains how many people will be in the study, who is eligible to take part in it, what study drugs or other interventions will be given, what tests will be done and how often, and what information will be collected. (NCI's Dictionary of Cancer Terms).
R	
Randomization	The process of assigning clinical trial participants to treatment or control groups using an element of chance to determine the assignments in order to reduce bias. (Source: NIH, NIA Glossary of Clinical Research Terms)
Recruitment	Active efforts by investigators to identify subjects who may be suitable for enrollment into a clinical trial. Subjects are selected on the basis of the protocol's inclusion and exclusion criteria during the clinical trial recruitment period. In multicenter studies, each investigator has a recruitment target or defined number of subjects to be recruited (Source: FDA, n/a)
Recruitment plan	The plan that outlines how individuals will be recruited for the study and how the study will reach the recruitment goal. (Source: NIH, NIA Glossary of Clinical Research Terms)
S	
Secondary endpoint(s)	Result(s) 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).
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)

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