How-To Guides for Patient Engagement

PATIENT FOCUSED MEDICINES DEVELOPMENT

How-to guide for patient engagement in the early discovery and preclinical phases

This How-To guide is part of a series of PFMD How-To guides that have been co-created in a multi-stakeholder environment built with the Patient Engagement Quality Guidance as a starting point. All How-To's are connected and provide a full set of instructions on how to involve patients across the research, development, and delivery of medicines

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

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Key terminology used in this How-To guide

Early discovery and preclinical

The authors' intent is for this How-to Guide to encompass the full spectrum of biological/chemical research leading up to clinical research and, for this reason, we choose to use both terms "early discovery" and "preclinical".

Early discovery involves molecular scientists who look at the biology and chemistry of the compounds to determine which to progress (FDA, 2018), while **preclinical** scientists may work with animal models to assess the safety of potentially viable compounds after the early discovery phase (FDA, 2018). Throughout this work, we will use 'preclinical research' to refer generally to these early stages and will define further where applicable.

Patients

The term "**Patients**" (with a capital **P**) is used in this guide as a general term for those individual patients, caregivers, and family members that are part of or engaged with the research team. When patients are referred to without capitalization, we mean the patient population in general.

- **Individual patients** - People having or at risk of having the medical condition(s), whether they currently receive medicines or vaccines to prevent or treat a condition (NHC & Genetic Alliance, 2017)

- **Caregiver** (or carer, or care partner) - For purposes of this How-to Guide, the term "caregiver" will refer to an "adult family member [i.e parents, spouse, partner, sibling] or other individual who has a significant relationship with, and/or who helps a patient with their daily activities, healthcare, or any other activities that the patient is unable to perform by him/herself due to illness or disability, and who understands the patient's health-related needs.

  This person may or may not have decision-making authority for the patient and is not the patient's healthcare provider." (FDA).

Patient engagement (in place of 'patient involvement' or other terminology)

In this How-to Guide, the term 'patient engagement' refers to the active and meaningful involvement of patients in developing medicines and it is used as a general terminology for readability and inclusiveness purposes.

- "Patient engagement occurs when patients meaningfully and actively collaborate in the governance, priority setting, and conduct of research, as well as in summarizing, distributing, sharing, and applying its resulting knowledge." (Canadian Institutes of Health Research, 2019).
- "INVOLVE defines public involvement in research as research being carried out 'with' or 'by' members of the public rather than 'to', 'about' or 'for' them." (NIHR Involve, 2017)

*** Patient engagement is NOT simply informing patients, surveying patients, consulting patients, or having patients participate in research. It means working WITH patients.**

Patient organization (in place of 'Patient group' or 'Patient advocacy organization')

In the context of this How-to Guide, the term 'patient organization' is used as a 'catch-all' phrase to include all patient groups and patient advocacy organizations in general. "[A] patient organisation is defined as a not-for-profit organisation that is patient-focused, where patients and/or care partners (the latter when patients are unable to represent themselves) represent a majority of members in governing bodies" (European Medicines Agency, 2018).

Researchers

The term "**Researchers**" (with a capital **R**) is used in this How-to Guide to refer to the Research team involved in the early discovery and preclinical research and it includes the different research settings such as academia, pharmaceutical, medical device or biotech industry, clinical research organisations, but could also include profiles such as clinical research associates (CRAs), research healthcare professionals, data managers, and study coordinators (Baer et al., 2011)[1]. The term 'researchers' (without capitalization) is used to refer to researchers in general.

[1] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3092661/

Introduction and overview of the work

Patient Focused Medicines Development (PFMD) aims to improve global health by designing the future healthcare with patients. PFMD focuses on making patient engagement a systematic reality by co-creating needed resources for all stakeholders to embark on and improve their patient engagement journey.

This How-to guide is part of the How-to Guides series[2] that build from the Patient Engagement Quality Guidance and provide a step by step recommendation to involve patients in specific activities and/or phases in the drug development continuum.

Each guide is a standalone tool, but can be combined with each other to form a comprehensive roadmap for patient engagement activities. Used together with the Patient Engagement Quality Guidance, it will increase the level of meaningful engagement with patients, improve the relationship between stakeholders and hopefully improve research outcomes overall due to having patients as research partners. These How-to guides are co-created with Patients, Researchers and other relevant stakeholders in the specific phases or activities.

This How-to Guide specifically focuses on the early stages of research. More PFMD's co-created resources can be found from the Patient Engagement Management Suite[3]- a comprehensive and interconnected guidance and tools for patient involvement and engagement.

Rationale and scope of this tool

Patient engagement has become commonplace at various stages in the drug development process. Yet this does not include the earliest stages, where limited evidence of patient engagement has been found to date.

This is despite a growing swell of evidence that patient contributions during the early discovery and preclinical stages of research can have a positive impact on research and trial outcomes.

Through such partnerships, researchers and patients may share expertise that helps with the prioritization of drug discovery projects. In addition, they contribute to the identification or prioritization of unmet patient needs, jointly substantiate a Target Value Profile (TVP)[4], and "translate" the symptoms and other manifestations patients experience into real scientific questions for researchers to work on in view of a new treatment. Last but certainly not least, these collaborations strengthen the empowerment of patients (Florin & Wandersman, 1990)[5].

Engaging patients "as early as possible" is recommended to improve research outcomes, de-risk early science, and avoid systematic errors, reputational losses, and further disinvestments (FasterCures,

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

[3] Access at https://pemsuite.org/

[4] Target Value Profile is an important document that guides the early development work and is described further in Book 1 - section 4 of this How-to Guide and in the glossary at the end.

[5] Access at https://link.springer.com/article/10.1007/BF00922688

2019), (Levitan et al., 2017)[6]. It is vital that the pharmaceutical industry, as well as regulators and other health system entities, recognize and accept the importance of patient input in early drug development.

Figure 1. Patient engagement is beneficial for both Researchers and Patients at any stage of research, however, there are more opportunities to benefit the research when Patients are involved as early as possible.

This step-by-step guide is designed to support research teams, patient communities, and other stakeholders to do more patient engagement in the early research stage. At present, there is a mutual need for Researchers and Patients to learn and develop the skills for patient engagement from the outset or early phases of the drug development process. For example, knowing the unmet needs of the therapeutic area before embarking on the development process is a key part of this phase.

[6] Access at http://www.nationalhealthcouncil.org/sites/default/files/FasterCures-PDUFA-Comment-Letter-FDA.pdf and at https://pubmed.ncbi.nlm.nih.gov/29714515/

Who is this How-to Guide for?

This How-To Guide has been developed by a **multidisciplinary working group**[7] to aid all stakeholders wishing to improve their patient engagement practices within the early discovery and preclinical phases of the development continuum. Preclinical study design can come in many different forms and proper planning at the start can be of significant economic value.

This tool is primarily designed for and with all relevant stakeholders in mind: Researchers across all sectors (academia, pharmaceutical, biotech), patients and caregivers, and patient organizations (see Figure 2). All these perspectives bring value to the preclinical research process to ensure that from the very start medicines are developed to meet patient needs' and preferences.

Figure 2. Relevant stakeholders in patient engagement in the early stages

Payers *should be involved once the discussion starts about an unmet medical need or an undertreated disease area. They will put the economical value on the final drug the drug is considered to properly respond to the societal/medical unmet need. This is why it is important that all stakeholders define from the beginning what is KEY from their perspective. Understanding the payer's objective informs the choices to be made regarding what needs to be demonstrated, even at the early stages.*

Research funders *are involved as a funder and to promote patient engagement in the early research stages.*

Ethics committees *have also an important role in this stage as they approve the development of any pre clinical research project.*

[7] See Acknowledgements to read more about the contributors to the PFMD Working group that co-created this How-to Guide

How to use this tool

This How-to Guide should always be used in a way that is relevant and applicable to the project at hand. The sections are standalone and can be used in whichever way or order is the most appropriate or helpful.

This How-to Guide (as 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 help in taking others' expectations into consideration and managing them. See Annex 1 for more details and links to resources related to PEQG.

Figure 3. The 7 Patient Engagement Quality Criteria

The sections in this tool

This tool has been divided into two 'books': Book 1 contains the main How-to sections, which align with the early discovery and preclinical research processes; and Book 2 provides the additional resources and considerations for the recommended approaches in Book 1. In addition, there is a dedicated Annex for each of the sections in Book 1 that provide a breadth of additional information and resources for each topic.

BOOK 1
How-to guide for patient engagement in the early discovery and preclinical phases

SECTION 1
Preparations for setting up partnership and collaboration: focuses on the importance of preparations to ensure that long term partnerships with patients are created and nurtured.

SECTION 2
Understanding the (medical) condition profile and therapy area: focuses on understanding the condition and finding gaps in the current clinical care and therapies available, helping to define unmet needs.

SECTION 3
Developing research methodology: focuses on working with patients to evaluate and identify the optimal approaches to address research objectives (both in the laboratory and clinical research).

SECTION 4
Target Product and Target Value Profiles: This is the last section and also the outcome from the previous sections (and the research process). It includes the rationale and instructions on how to create a target value profile that represents the patients' perspective on the product.

BOOK 2
Practical considerations and details to organize meetings with patients

This part of the How-to Guide collates all practical considerations for the recommended approaches in Book 1. Book 2 can be also used as a standalone reference when organizing patient engagement activities as recommended in Book 1.

These practicalities can be adaptable to patient engagement in other phases or activities and do not have to be strictly considered only in the early stages.

How-To Guides for Patient Engagement

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BOOK 1

How-to guide for patient engagement in the early discovery and preclinical phases

Table of content

How-To guide for patient engagement in the early discovery and preclinical phases

This step-by-step model for patient engagement in the early stages (figure 4) intends to show the ideal order in which the activities are taken and potentially repeated if the situation requires. **Patient engagement activities at any stage should always start as early as possible. In this case, when the Researchers begin to understand the condition area.**

Patients can start to uncover the burden of the condition, possibly also of previous or current treatments. Each step of the spiral model is explained in the following sections with more details provided in the dedicated Annexes, at the end of this How-to guide.

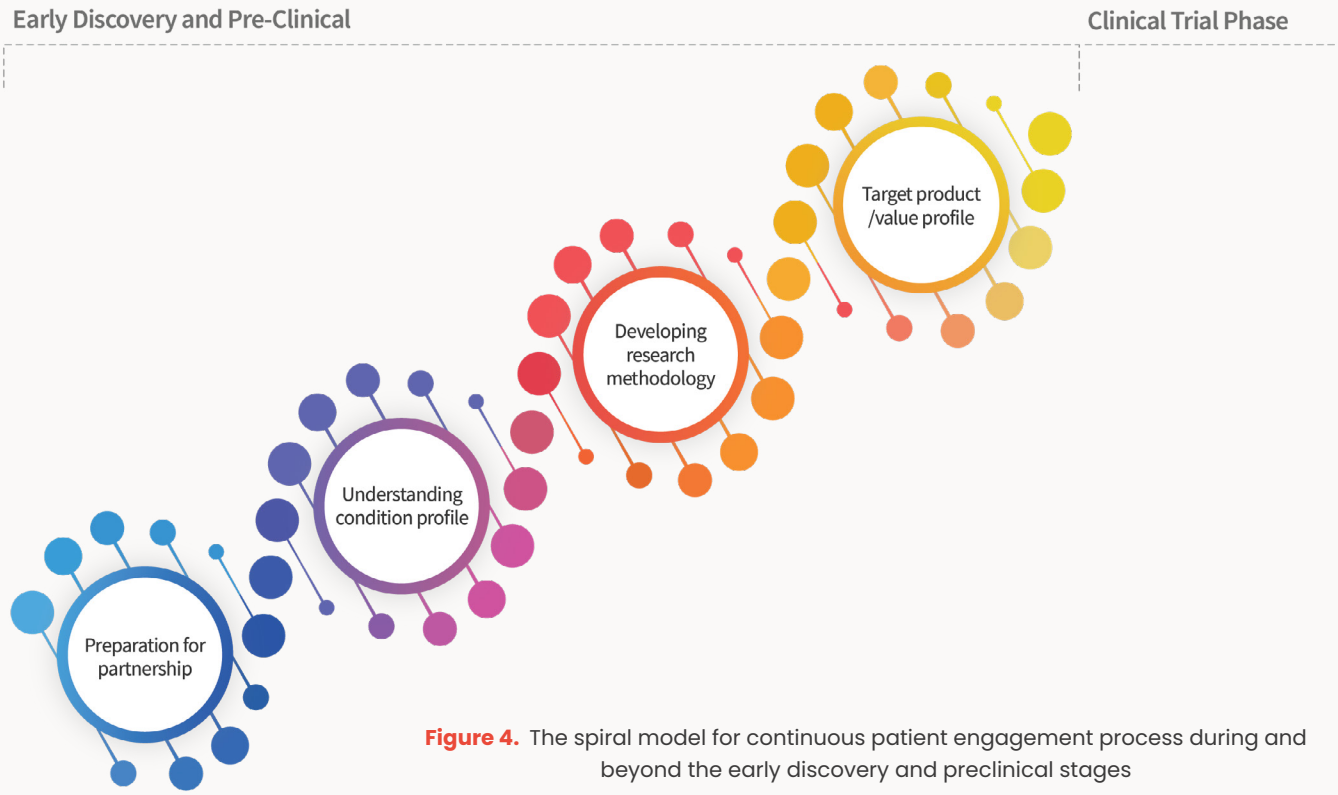
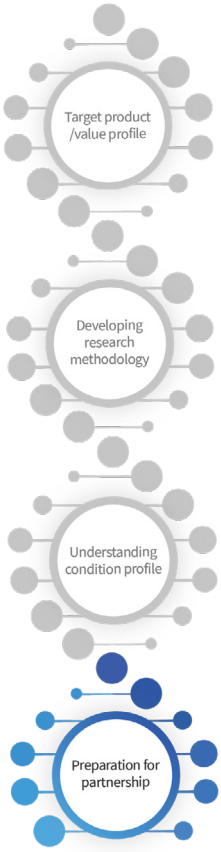


Figure 4. The spiral model for continuous patient engagement process during and beyond the early discovery and preclinical stages

Note

For those who have never been involved in patient engagement in the early stages, we recommend reading through all sections in Book 1 and following the model step-by-step if applicable.

1. Preparations for setting up partnership and collaboration



The goal of this step is to:

- **Identify opportunities** for Patients and Researchers to work together during the early discovery and preclinical stages of research. This will set the stage for future collaborations and hopefully prevents tokenistic and one-off patient engagement approaches;
- **Prepare patients** for patient engagement activities by providing educational tools and resources about drug discovery and preclinical research, in recognizing that this may be a new area for many;
- **Prepare the Research team** for a meaningful, effective, and respectful interaction with the patient, and give them tools to build a mutually beneficial long-term partnership;
- **Co-develop a patient engagement plan** to understand the patients' perspective on unmet needs and preferences and how patients wish to contribute to drug development's initial steps.

1.1 Identifying opportunities to work together

There are different ways in which initial conversations about patient engagement in early discovery and preclinical research may arise between Patients and Research teams. Researchers 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 early-stage 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. At these early stages, where patient engagement is not yet commonplace, it is important to keep an open mind and be prepared to embark on new working methods never tried before. Stakeholders should work together to scope ideas and opportunities, and agree on a shared purpose for the collaboration. After establishing mutual interest between Patients and Researchers, activities to clarify the goals of the collaboration for both partners include:

Researchers:

- Conduct internal discussion to identify the preclinical research team that will implement patient engagement in preclinical research;
- Establish project-specific goals of the endeavor;
- Define the timeframe of the preclinical development stage and consider when this dialogue should start;
- Identify leaders for collaboration (i.e. who leads internal activities, liaise with the patient organization, etc.);
- Identify key stakeholders to be involved in this stage, to provide a balanced insight into the condition and therapeutic area;

- Conduct internal discussion on how insights gained will be integrated and communicated to internal stakeholders;

Patient organizations

- Establish patient-specific goals of the endeavor;
- Enable underrepresented patients due to systematic bias provide input by ensuring diverse representation across and within patient organizations;

Researchers and patient organizations

- Use the PEQG to help plan the project and review the considerations relevant to it;
- Discuss and agree on the shared purpose within the research project and the stakeholders to be involved to reach the common goals;
- Commit to transparent, respectful, and continuous communication during the project;
- Identify respective leaders for collaboration (leads internal activities, liaises with the research institution and the patient organization);
- Define the responsibilities of all contributors;
- Identify if Researchers and Patients need additional support or capacity building to properly engage and collaborate (both).

Note

See Annex 1 for further information and guidance on considerations when developing relationships.

1.2 Preparation for patients and patient organizations

Managing expectations:

- Patients and patient organizations need to be aware that drug development is a long and uncertain process.
- The early discovery and preclinical stages of research involve testing many different possible drug candidates and potential treatments, most of which do not enter clinical development. There are many reasons why a potential treatment does not advance to the clinical research stage (studies that involve people).
- Even if preclinical research does not progress to clinical development, the knowledge and insights gained from patient engagement activities during the early stages are still very valuable. Patient engagement is also very motivating for Researchers and having a sustainable plan for patient engagement will ensure those insights are used to shape future research work.
- A key aspect of patient engagement at the discovery and preclinical stages of research is working together to understand how patient preferences and needs can be translated into a scientific reality. There will be times when this might not be possible to achieve.
- The goal of patient engagement is to work together to determine what is a 'must-have' compared to 'nice to have' within the scientific capabilities of the research.
- It is important to note that a Researcher's perspective cannot be assumed to reflect all Researchers.

Timelines and resources required:

- 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, Research teams might be struggling with tight deadlines which in turn might translate into unrealistic timeline expectations towards patient organizations and patient engagement activities.
- It is also important for Patients to understand that research might take time and resources and projects might extend beyond the original estimates. See one example of a the full R&D process in figure 5. Whatever the case, concerns should be possible to voice at any time during the project; either to the Researchers or patient organizations involved.

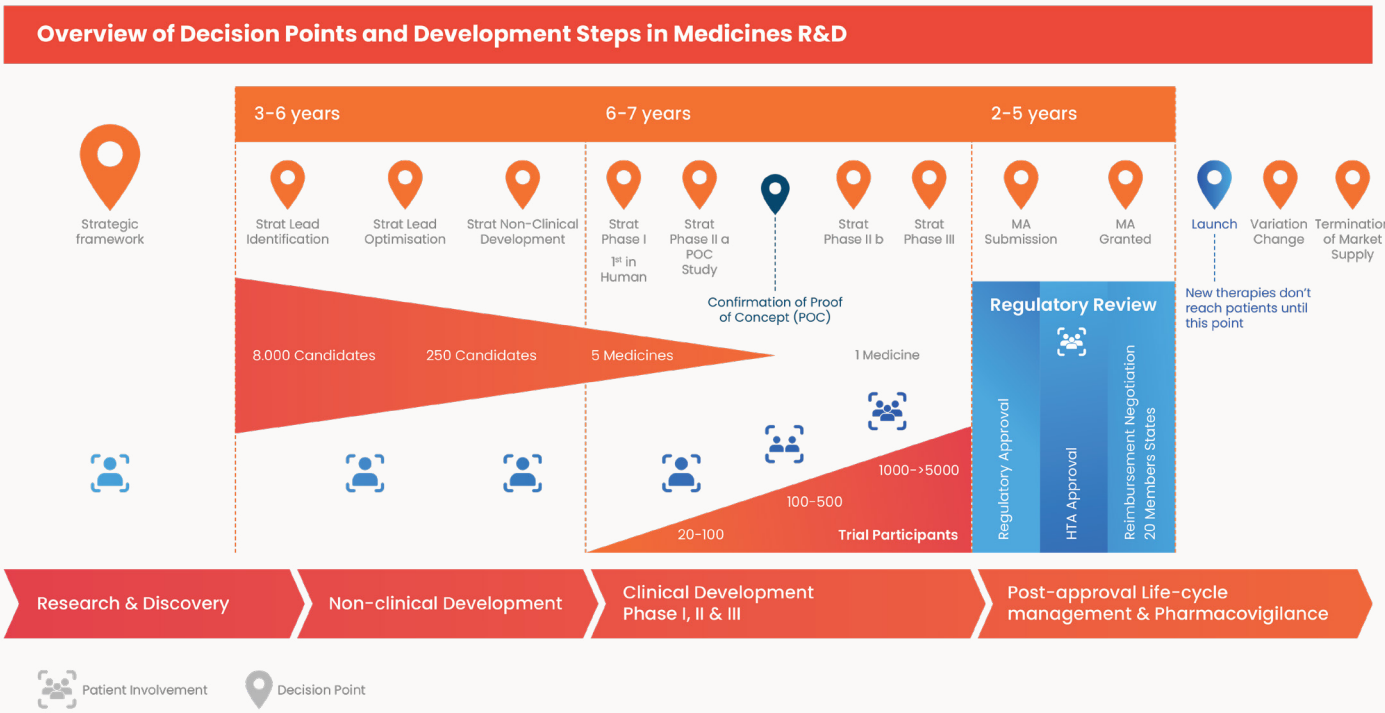


Figure 5. Overview of decision points and development steps in medicines R&D from EUPATI[8]

1.3 Preparation for Researchers

Resources and time required

- Ensure to have the necessary resources required to support patient engagement activities - consider the people, time, and funding needed to engage with patients, caregivers and patient organizations.
- Researchers must be as transparent as possible with the Patients and patient organizations

[8] European patients' Academy (EUPATI), 2015. Available: https://toolbox.eupati.eu/resources/discovery-and-development-of-medicines/

they work with about timelines. This will facilitate reaching an agreement on timescales that suit all involved.

- 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 Patients and patient organizations within the project.

Respect and accessibility:

- Minimize the use of jargon when communicating and use plain language for all materials as far as possible. Note that terminology used in early drug discovery and preclinical research might not be familiar to many people. Extra time and effort may be needed to ensure that materials and communications are clear.
- Work together to agree on and set-up the appropriate confidentiality agreements, ensuring that they are clear to both parties.
- **Collaborating with a diverse group within the patient community is strongly encouraged to gain a robust and representative understanding of the community's views, hence making informed decisions.** It's important to ensure patient engagement activities are made accessible for all, and that engagement is not limited to patients who have a scientific background.
- It is important to note that one patient's perspective cannot be assumed to reflect all patients.

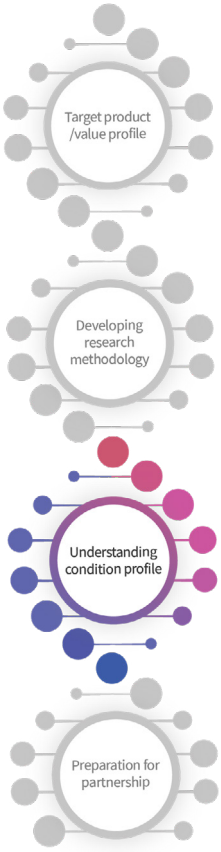
1.4 Co-develop a patient engagement plan

To ensure a productive relationship, all stakeholders must be open to feedback and ready to actively collaborate to reach the common goal. Co-developing a patient engagement plan, using the Patient Engagement Quality Criteria, will help define the goal(s) and the steps needed to achieve these.

The following considerations are good to start with:

- Consider that Patients and Researchers should define together the Shared purpose and Transparency in communication. It will help the agreed common goal and clarify the methods for collaboration.
- Ensure that roles and responsibilities are clear for all stakeholders involved and accessible throughout the project. Consider including representation from in-house teams across the drug development process so that the end-to-end needs can be better understood and the transition and learnings of the patient engagement efforts will progress without interruption through the process.
- Consider the need for capacity building:
  - Ensure that the Research team feels confident in meeting with Patients. For example, for people living with dementia or pediatric patients, a facilitator from the relevant patient organization may be needed to advise the research team on how to conduct interactions to create a trustworthy and meaningful experience.
  - Ensure adequate capacity for engagement from the patient community side.
  - Ensure a diverse representation from the patient community and that the research team is comfortable/confident with potential cultural differences.

2. Understanding the (medical) condition profile and therapy area



Rationale

In order to focus on research that will develop treatments that matter to patients, Researchers must understand the patients' experience with a disease. This includes patient burden, experiences with treatments and aspirations for better treatments. Assuming the discussion occurs at a stage where at least some target diseases are identified for the development of therapeutic solutions, this activity reveals to Researchers the Patients' experience and perspective on what it is like to live with the condition under study and what might be the unmet needs. This knowledge helps to focus the preclinical research team on the symptoms that matter most to Patients. This activity creates a win-win situation for Researchers and Patients in two ways:

- **Researchers will learn**, early in the drug development process, directly from patients about the condition – experiences, concomitant therapies, medication, preferences, and other information that do not appear in the medical literature.
- **Patients will benefit** by being able to share their unique perspective on living with the condition to uncover unmet needs. This helps define how and where their experience can be improved, including understanding the research being conducted on their condition. They will also feel heard and appreciated - that their perspective is taken seriously, facilitating their engagement in the project. Having this dialogue with researchers gives Patients more hope for future solutions really solving their health problems.

The collaboration between Patients and Researchers in this section is done through a Patient-Researcher Exchange Meeting described further below (figure 6). **There, Patients have a chance to meet with the Research team to share their experience living with the condition as well as to learn about ongoing preclinical research.**

Goals in this activity are to:

- **Educate the Research team on Patients' experiences and perspectives** of the condition[9]. Gather patient input to educate Researchers about:
  - The patients' symptom burden and impact on daily life;
  - What therapies do patients use;
  - The burden, efficacies, or lack thereof, of the therapies ;
  - The patients' views on an ideal therapy (including mode of administration and site of care);
  - Understanding patients' views on risk-benefit, trade-offs (e.g., potential side effects, quality of life) and whether they will accept new treatments;
  - Uncovering the patients' unmet needs.
- **Act as an initial dialogue between patients, research teams, and other stakeholders** (i.e., clinical development professionals) towards creating a long-term relationship across the drug development process.

[9] It is essential that the Research team has established the target condition before reaching out to the patient community. See Annex 2 for tips on gaining this basic level knowledge.

2.1 Organizing the first Patient-Researcher Exchange Meeting

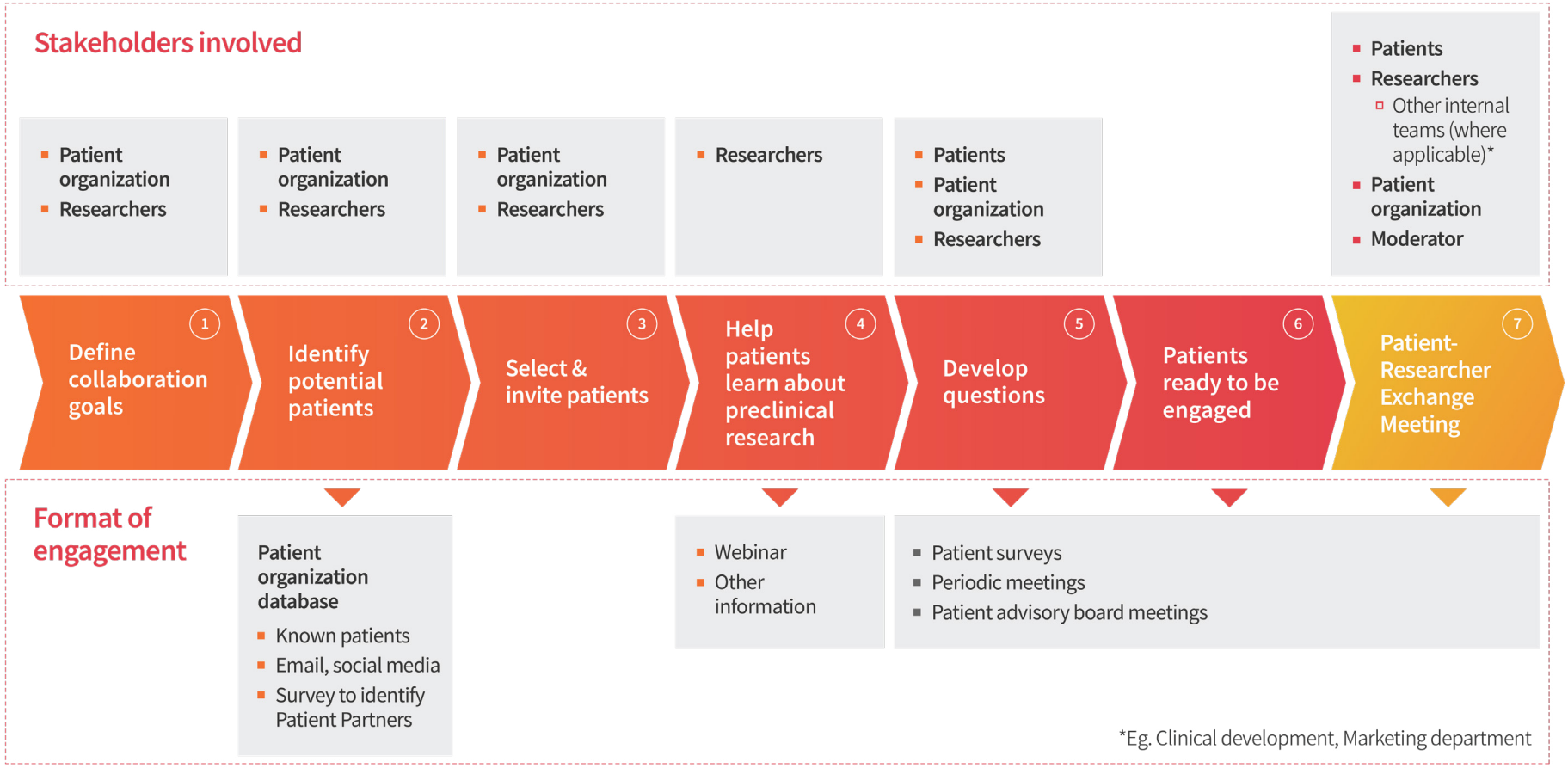


Figure 6. The path to organizing the Patient-Researcher Exchange Meeting

The Patient-Researcher Exchange Meeting is the first (team) meeting that aims to educate Researchers and Patients and create a collaborative relationship. This Patient-Researcher collaboration should be dynamic and continuous, not a one-off event.

The Patient-Researcher Exchange Meeting offers Researchers an opportunity to gather patient input. The meeting's structure is inspired by the PFDD meetings started and continued very successfully by the US FDA (FDA, 2016)[10], but contains additional activities.

Both Researchers and Patients benefit from the interaction, which optimizes chances to foster strong patient engagement. Other strong rationale points behind this format of exchange meeting are:

- Opportunity for the Research team to gather patient input by seeing each other (in-person or virtually).
- Patients' testimonies inspire thought by patients before the actual meeting; patients will be well prepared for discussion.
- Group discussion facilitates the showcase of experiences and generation of ideas (intra-group synergism).
- Utilization of "story circles" and other innovative and projective techniques allow Patients to openly share their lived experiences.
- A moderator can follow up and probe deeper to elicit information that is important to drug discovery.
- If conducted as an in-person meeting, the site for holding this meeting should be mutually agreed upon. Organizing it at the Researcher's site could show the team's commitment to transparency, giving Patients in-person exposure to preclinical research. It may also elicit more patient investment.
- Seeing faces (in-person or virtually) deepens & enriches the Patient-Researcher relationship.
- Allows the Researcher to start building a long-term relationship with the patient community.
- Such a program will fully engage, inform, and motivate both parties, towards cementing the relationship and providing high-quality information.

Find out about practical instructions and considerations for organizing this meeting in Book 2.

2.2 Co-developing discussion questions with patients

Co-creating questions provides the research team with direct patient insights on the condition experience. Because patients know best how they prefer to be asked about their condition, they should be consulted regarding such questions. Involving patient organizations and patients (usually in a steering group) in shaping these questions, can make them feel that their opinions matter and are respected, promoting effective engagement. It also helps respect the cultural differences and

[10] Format to collect patient input by testimonies, moderated discussion and polling questions has been validated in US FDA Patient-Focused Drug Development (PFDD) and Externally Led Patient-Focused Drug Development Meetings. Find out more about these meetings from: http://www.fda.gov/downloads/Drugs/NewsEvents/UCM493616.pdf

intercultural communication particularities in addressing certain topics and in the way questions are formulated[11]. Patients involved in the creation of the questions should be different than those participating in the survey or meeting. It may therefore be useful to establish an opportunity for patients participating in the survey or meeting to provide information that they feel is important for the preclinical team to know but that did not otherwise surface. This can help uncover information that may be important across a broader diversity of patient experience than that represented by the patient involved in the co-creation of materials.

How to co-develop the questions

The suggested condition-related questions in Table 1 below have been used in EL-PFDD[12] meetings with the US FDA. Many of these topics were generated by the FDA to gather patient input. More detailed sets of questions can be found in Annex 2.

How should patients be questioned to evoke patient insights to meet the needs of the research team? (Patients steering committee can help shape questions for patient participants)
The questions should cover the following topics: • living with the condition (symptom burden, effects on daily life, fears); • challenges to treating the condition (efficacy of current treatments, compliance); • risk-benefit, acceptable trade-offs regarding side effects; • preferences regarding clinical trials.

Patient organizations or Researchers and Patients should work together to co-define these questions.
Example of questions for this dialogue:
• What questions should we ask so we understand your views on:
  ○ The most burdensome symptoms you experience and how have they changed over time.
  ○ The greatest impact on the quality of life.
  ○ The treatments you have taken, currently take or aspire to take (ideal therapy).
  ○ Your preferences on how a drug is taken (e.g., pill, injection, etc.?).
• Should we ask:
  ○ open-ended questions;
  ○ scenario-based questions (e.g., 'If you could choose between two drugs, one that…');
• What information would help you to answer a question on …?

Patients review existing questions, then they are asked, "Is there anything else you feel comfortable sharing with us about your experience living with your condition?"

Table 1. How to co-create questions with patients

[11] For more resources on intercultural communication in health, check Annex 6

[12] EL-PFDD = Externally Led Patient-focused Drug Development

2.3 Gap analysis

Gap analysis is the process of identifying 'what is currently missing' so that it can be addressed. This can apply in terms of knowledge (e.g. understanding of patient burden) or a product (e.g. characteristics that the standard of care lacks). This focuses further work to address such gaps.

Rationale

By involving patients early, Researchers can use patient input to identify the gap between existing care and the current patient experience. It is important to involve all relevant stakeholders that can contribute to the analysis from different perspectives, to help form a comprehensive picture of the needs, including unmet needs.

For example, rheumatologists and nephrologists should be talking to each other because on many occasions, kidney condition is caused by immunological problems. However, as a preset, these two specialists are not interacting with each other in the care of their patients.

Goals

The gap analysis looks to achieve two goals:

- Identify potential gaps between the current standard of care and the patients' needs and preferences.
- Understand patient experience and preferences to help to identify preclinical candidates or prioritize preclinical research directions, especially regarding side effects, risk-benefits, and/or patient outcomes.

A preliminary understanding of the potential gaps and unmet needs should naturally emerge because of understanding the patients' preferences, needs, and burdens within the condition profile. This understanding must be cross-referenced with knowledge of the existing current care options. Additionally, all this must accompany the Research team's understanding of the condition and therapeutic area.

The Research team might hold meetings where healthcare professionals (HCPs) and Patients interact in order to see each other's perspectives on the gaps and stimulate conversation around differing viewpoints. Identify the right stakeholders needed by asking: *What type of HCPs are involved with the specified therapeutic field of study and is used by the patients?*

Examples of relevant questions

To help identify potential gaps in clinical care[13], the following example questions may be asked to patients:

- Do you feel that your physician is providing as much information to you about your health as you want?
- Are all of your doctors talking to each other as much as you would like?

[13] With **gaps in clinical care** we mean what patients see as unmet needs in their care.

- Are your current doctors bringing in the right specialists to help address all the health concerns that are important to you?
- What frustrates you the most about the way you currently receive care?
- Toward understanding your thoughts on the gaps in care that you experience, what question do you wish your doctors and pharma companies asked you, but no one does?

2.4 Priority setting

After the gap analysis is concluded and before the research methodology is developed, the Researchers should set the research priorities with Patients. Priority setting helps focus the research team on the key needs identified as important to patients. Some challenges in priority setting remain and can be grouped as follows:

- **Identifying potential for priority setting within the research cycle**
  - Numerous exercises for research priority setting exist involving patients, caregivers and patient experts. These exercises utilize a variety of different methods and tools.
  - There are many possibilities to integrate priority-setting exercises during the development of research projects. The challenge remains to identify the appropriate time within a research project to implement the exercise.
- **Priority setting granularity**
  - When conducting a priority setting exercise, the level of detail to be discussed is essential for further processing and implementation.
  - This level of detail can range from defining wide themes of discussion to identifying research questions.
- **Facilitating research priorities**
  - When conducting a priority setting exercise, consider how to best facilitate the process during and especially after the research priorities have been identified. This will maximize the impact of prioritization.
  - To achieve relevant research priorities for all stakeholders, the involvement of the Researcher's institution is necessary because the project has to be implemented in accordance with the regulations and programs of the institution to be carried out effectively.

Methods and best practice examples regarding priority setting can be found in Annex 2.

3. Developing research methodology

Rationale

It is vital to let Patients know that what they say matters in the research approach. This integrated and thorough planning will ensure that research answers questions relevant to the daily burdens faced by patients and caregivers.

Patient engagement activities at this very early stage can substantially shape the approach from which research is conducted. Early-stage patient engagement can lead to early adaptations of research with more patient-focused study designs, the ultimate objective leading to treatments and services which patients want and need.

Patient engagement helps prioritize the research questions on which laboratory work should focus on. Laboratory scientists focus on specific scientific aspects of a project, which may or may not be the most relevant for people with a condition. Something that may be interesting to investigate from a scientific perspective may not be the issue that most matters daily to the people affected by the condition.

Goals

The aim of patient engagement in advising the research approach is to recognize how patient insights can inform scientific work and not to train patients to become scientists. Patient input regarding symptoms or disease burden may provide direction for the preclinical research focus. This permits drug development to focus on what is important to Patients and caregivers, ultimately improving their daily quality of life and their long-term contribution to society.

The goals in these sections are to inform how to:

- Work with Patients to evaluate the optimal tools and approaches to address research objectives in laboratory-based and virtual (in silico) studies.
- Work with Patients to evaluate possible studies to address clinical questions and unmet needs.
- Gain an understanding of the disease and generate patient-focused insights which can ultimately facilitate the development of outcome measures for future clinical studies.

3.1 Considerations for developing a patient-focused research approach

In some cases, there will be a need to train researchers, statisticians, etc. on patient engagement (e.g., those who may not have worked with patients before), and depending on the patient community, special considerations may be needed for these interactions. The training necessary will be decided on a case-by-case approach (see section 1 - Preparations for collaboration).

In addition to any required training, there are some basic requirements for ensuring that the patient voice is heard and understood in all research projects involving Patients.

These include plain language draft research questions, research plans, which include potential research approaches and measurement tools. Ideally, these should be ready for the interactions with Patients in order to gain input in how to finalise these plans.

3.2 Key activities relevant for this stage

Several engagement activities are relevant in the creation of research approaches and can be used to gain different kinds of patients' insight depending on the aim and scope of the research.

Researchers may consider some of the methods outlined in Book 2 (section 'Format options for meetings') when thinking about how to gather patient input. When planning a patient engagement approach, a systematic and simple process should be followed, an example of which is found below.

- Appoint a project steering group to oversee the collaboration between the research group and Patients.
- Organise and conduct a Patient-Researcher Exchange Meeting to initiate the Patient-Researcher dialogue. This may include laboratory visits if safety (i.e., COVID-19) can be assured.
- Create a virtual laboratory or simulations (such as videos to illustrate what research is like).
- Consider the size of discussion groups - smaller groups can work better.
- Face-to-face discussions and one-to-one conversations work particularly well for complex topics.
- Peer-to-peer education can be powerful (e.g., a buddy system with Researchers, Patients) to support those involved throughout the project.

3.2.1 Possible topics for discussion

Outcomes measures

Use discussions to:

- Outline how things are measured at an early stage and why researchers measure different things.
- Discuss and evaluate how a preclinical finding may relate to a real life patient situation.
- Identify what outcomes are important to patients and how early research can or cannot take this into account.

Identify the most important factors for a patient to take the medication

Use discussions to:

- Clarify the formulation of the drug and discuss how this affects patient's experience of taking the drug.
- Understand the patients' preferred route of administration.
- What is behind this choice and what benefits does this new route of administration give to the patient and caregiver?

- Discuss adherence, usability, and patient experience.
- Discuss site of administration: physician's office, infusion suite, home, etc.

The use of animal models vs. cell models, human tissue etc.

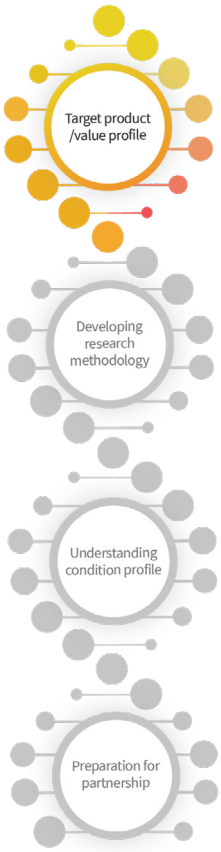
(Animal models need to be used for safety testing, but they can also be used to test the efficacy of drugs. Other types of models can also be used to test safety and effectiveness.)

Use discussions to:

- Inform people about how and why animal models are used.
- Inform people about other models of testing.
- Discuss how the use of different models may or may not relate to clinical outcomes, and prioritise testing in different models in relation to the outcomes that are most beneficial for patients.

Find more published evidence of patient engagement at the bench and examples of how patient engagement can be used by researchers in this step in Annex 3.

4. Developing the Target Value Profile/ Target Product Profile (TVP / TPP)



Rationale

A target value profile (TVP) is an essential part of early research in drug development. It helps companies and researchers plan the development of new medicine. The TVP is a consolidated set of "expected and minimally acceptable characteristics" of a chemical molecule, biological product, or medical device, used as treatments which are valuable and meaningful for patients by addressing areas of unmet needs.

Alongside business rationale, public health demands and other elements for decision making, the TVP informs the **target product profile** (TPP) – an updatable guidance for the drug developers with targeted characteristics of a potential product[14].

Goal

The correctly reflected and validated set of minimally acceptable characteristics of a future product has a significant impact on success at the earliest stages of the R&D cycle. This process determines whether an early research project should move forward or not based on clearly defined minimal acceptable characteristics. Therefore, the TVP - as a main element of TPP that encompasses core values and addresses unmet medical patient needs - should be co-developed with patients.

Patients' insights should form one part of the evidence base that supports the Researchers in advancing the research.

The full picture should be formed with patient insights and other scientific evidence such as previous scientific research, from literature, insights from other relevant stakeholders, etc. If patient insights are very disparate, more validation or insight gathering might be needed to help Researchers determine the patient preferences.

How to create a TVP/ TPP

Arriving at this step of the process means that Patients and Researchers have already established a working relationship and Patients are part of the research team. However, there is also a possibility that this is not the case and Patients are engaged for the first time only when creating a TPP.

[14] There exists a Guidance for Industry and Review Staff on Target Product Profile Development that was firstly prepared by the FDA's Centre for Drug Evaluation and Research (CDER) in 2007, however, this document does not provide any reference to Target Value Profile and possible patient's input (FDA, 2007)[15].

[15] Access at https://www.govinfo.gov/content/pkg/FR-2007-03-30/pdf/E7-5949.pdf

There are some principles for TPP/TVP development in the drug development process (that are shown in Figure 7):

- The TVP represents the culmination of the insights generated with Patients in the prior engagement activities. At a fundamental level, the TVP should state which aspects of disease burden would need to be reduced (and to what degree) to be a meaningful treatment option to the patient.
- The interactions leading up to the creation of a TVP should have involved several research projects with Patients to form an understanding of firstly the condition area, then the therapeutic area, existing gaps and potential medical needs that the current standard of care does not cover.
- The TPP and TVP are normally drug developer-oriented outputs and thus their creation can be assumed to be drug developer-led in most cases.

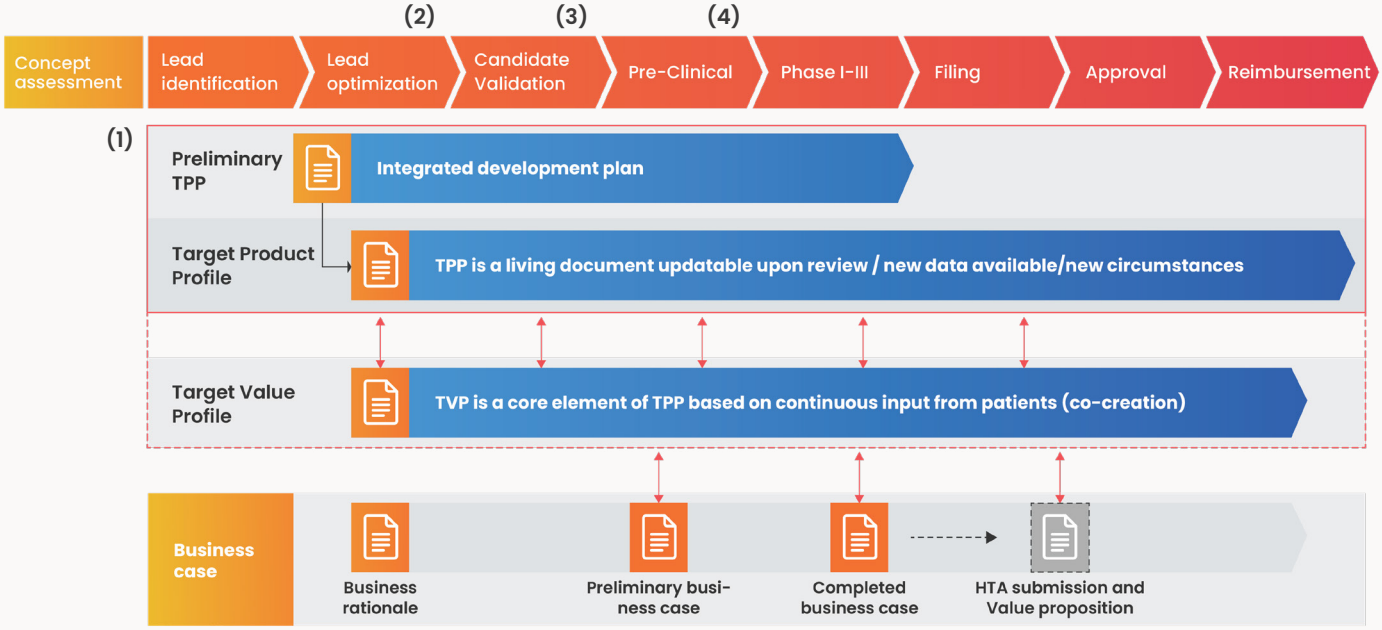


Figure 7. Key TPP/ TVP input milestones throughout the drug development continuum[16].

The process flow on the next page (Figure 8) shows how patient input feeds into the development of the TVP/ TPP along the early discovery process (following the steps in this How-to), but if Patients are engaged for the first time at the preclinical stage, the depicted patient engagement process can just be moved up and steps followed from left to right nonetheless.

[16] Explanation of Fig.4: (1) Preliminary TPP is approved upon concept assessment, prior to lead identification; (2) Full TPP and IDP approved upon lead optimisation, prior to candidate validation; (3) Upon candidate validation and prior to starting pre-clinical research (from this milestone forward, the TPP is a living document, which is updated whenever new data is available); (4) TPP updated with reviews at each step

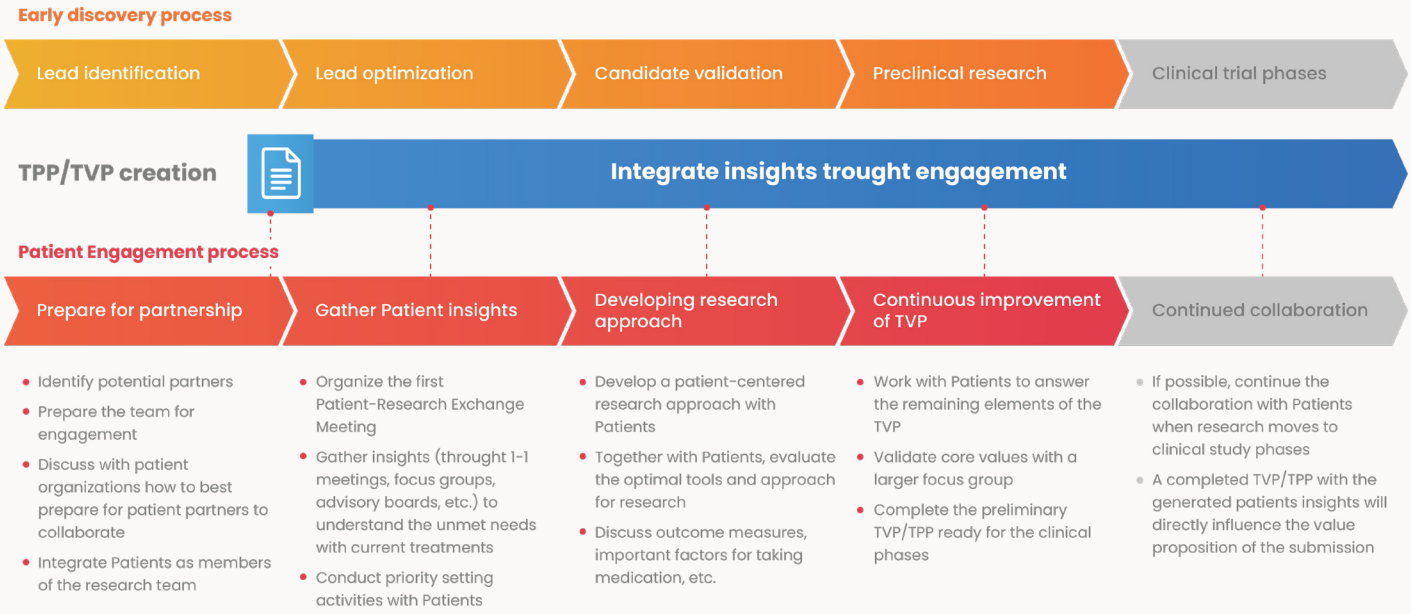


Figure 8. Implementation of this How-to Guide in the drug development process: gathering patient input to inform research.

4.1. Key elements of the Target Value Profile for patient engagement

The key elements of the TPP and respective TVP attributes with suggested validation/consultation topics with Patients are provided in the overview Table 2 on the next page.

The TPP elements are listed on the left column and suggestions to gain patient insights is described in the column on the right. The objective is to discuss with Patients and understand their opinions, needs, expectations and preferences regarding each of the elements of the TPP in order to respectively integrate key patient values in the TPP.

Patient insights for some elements will have been gathered through previous patient engagement activities or in the previous steps discussed in this guidance.

This table does not aim to be an exhaustive list of key elements and corresponding target value attributes, but gives a good overview of key topics. See the full TPP/ TVP table with specific questions for Patients to inform TVP attributes co-creation in Annex 4.

Turning TPP elements to TVP elements with patient insights Check the printable table with predefined questions in Annex 4	
TPP element	Extracting the value to patients (TVP)
Indication	Discuss with Patients what it means to live with the condition, its burden and what quality of life is. Ask about how current treatments are doing and how they are helping Patients to manage their condition.
Target population	Discuss the possible target patient populations for this medicine and how useful it could be. Include different perspectives to form a comprehensive picture of the potential target population and speak to relevant patient organizations to gain more insights of the demographics and epidemiology.
Efficacy and effectiveness	Ask patients of the effect the medicine should have on the condition and what might be the preferred frequency the medicine could be taken. It is important to understand also how the medicine could reduce a specific burden experienced by patients today (that current therapies might not address).
Resistance (for antimicrobial agents and some other medicines)	Discuss how taking this medicine will impact the ability to take other medications and manage other co-morbidities in the future as well as how fast could this medicine become ineffective.
Safety profile (side effects)	A side effect might be tolerable for 3 weeks and another for 3 years. OR a side effect might be tolerable until there is an important life event. Discuss with patients to understand what is important to them and what would constitute a meaningful improvement.
Tolerability profile	Discuss the scenarios in which certain side effects would still be tolerable for taking the medicine because its benefits are greater. And in which scenarios side effects would be a "show-stopper".
Clinical pharmacology	Gain insights on the current therapies patients are using and identify how this drug might fit in or impact the patient. Reach out to patient organizations to understand the comorbid conditions that might affect the target populations.
Dosage and administration (posology)	Understand the patients' preferences when it comes to dosage or administration of the medicine as this might greatly affect the usage. Find out what might constitute a meaningful improvement to current therapies.
Storage conditions (note that this might not be clear yet at this early stage)	Find out if the storage might be an issue to the patient or what difficulties in the storing of current therapies are posing.
Business rationale (business case – may/may not be a part of TPP)	Discuss with patients about how other meaningful factors around the medicine might affect patients' decision to use it. For example, consider if the healthcare system is set up appropriately to increase patients' access treatment when needed. Consider also cultural, social and ethical factors that might affect patients getting the treatment.

Table 2. Rationale for turning TPP elements into TVP with patient insights

How-To Guides for Patient Engagement

PATIENT FOCUSED MEDICINES DEVELOPMENT

BOOK 2

Practical considerations and other details for organising patient engagement activities

Table of content

Book 2 collates all practical considerations for the recommended approaches in Book 1 and can be used as a standalone reference when organizing patient engagement activities.

These practicalities can also be adapted to patient engagement in other phases and do not have to be strictly considered only in the early stages.

The main considerations are in the body of the sections in Book 2. Make sure to also explore the attachments, links and annexes at the end for provided checklists and other tools that might help in building rrelationships, planning and conducting engagement activities.

1. The path to the "Patient-Researcher Exchange Meeting"

The Patient-Researcher Exchange Meeting is the first meeting that aims to educate researchers and patients and creates the collaborative relationship. This patient-researcher collaboration should be dynamic and continuous, not a one-off event. The Patient-Researcher Exchange Meeting offers researchers an opportunity to gather patient input in a meeting whose structure is inspired by PFDD meetings started and continued very successfully by the US FDA but includes additional activities.

The goal of this activity is to:

- **Identify, select and invite patients** for the partnership activities.
- **Act as an initial dialogue between patients, research teams and other stakeholders** (i.e., clinical development professionals) towards creating a long-term relationship across the drug development process.
- The Patient-Researcher Exchange Meeting can lead to other collaborative activities.

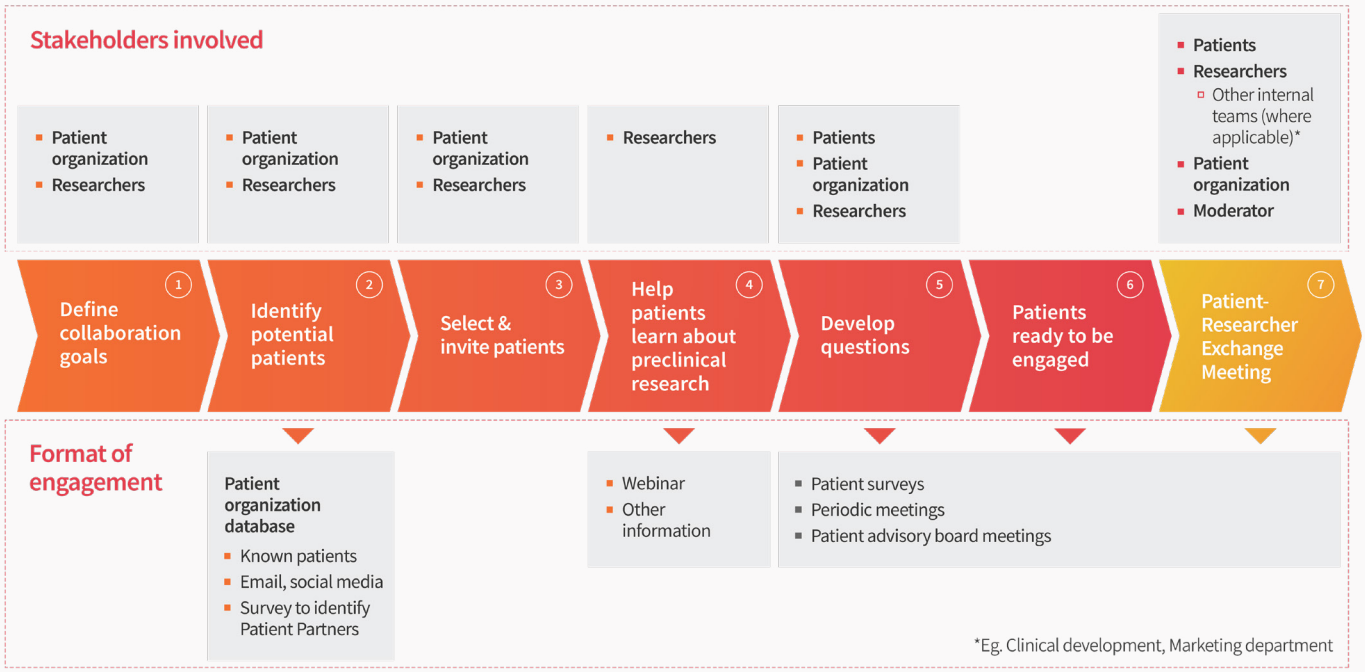


Figure 6 repeated from Book 1. The path to the Patient-Researcher Exchange Meeting

1.1. Define collaboration goals

Goals of the collaboration in the larger context should be defined together with Patients or relevant patient organizations if the patient partners have not yet been identified. Depending on the project

timelines and the potential of previously existing relationships with the patient community, the steps 2-4 in this pathway (Figure 6) might not be needed.

1.2. Identify potential patient partners

Rationale

This step bridges the gap between patient organizations and Researchers to set the stage for the selection of suitable candidate patients (for partnership).

Patient organizations know their patients and thus can often recommend to Researchers 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 representability of the global population.

In many chronic conditions with large numbers of patients, only a small fraction of patients are members of a patient organization; the great majority can be found in research centres and can be identified by physicians.

Goal

To identify a pool of patients from which to select final participants to the Patient-Researcher Exchange Meeting.

Target population

- Individuals who are motivated to:
  - learn how therapies are discovered/investigated in preclinical research;
  - participate in the project;
  - feel comfortable sharing their experience;
- Patients all along the clinical spectrum of the condition (see Patient Survey).
- Patients who have differential access to care due to underlying systemic bias (e.g. women, people of colour, gender identity).
- Care partners of adult and paediatric patients.
- At certain stages of the preclinical research project, subsets of patients (e.g. those in a certain stage of condition, exhibiting specific symptoms, post-organ transplant status, etc.) may be included.
- Representation by diverse demographic mix (age, gender, education, ethnicity, geography, etc.).

Suggested methods to identify Patients (as partners)

1. Patient Organisation* Identifies Candidate Patients for the Project

** When there is a patient organization/organizations identified in advance*

Finding potential patient partners can include, but should not be restricted to (in no particular order):

- Patient advocates identified from patient organization membership. These patients are experienced in speaking about the condition and represent a pool of potential

candidates that can be easily and rapidly contacted.

- Patients from the community, identified through the Patient organization's membership database or informed about the opportunity through dedicated social media (patient organization's Facebook followers, emails to members, other social media methods).
- Patient organization's outreach to potential candidate patients via a survey to identify patient partners[17] (see Figure 6) containing questions to identify those who fit the requested profile as co-defined in the Target Population.
- Patients respond to outreach; the responses are assessed and key patients identified by the patient organization.
- Patient organization or an unaffiliated third party mediates introduction of research team to interested patients.

Depending on the context or in case of no existing patient organizations (preferred partner) in the field of interest, other sources can assist research teams in recruiting participants for engaging patients in preclinical research (this list is not exhaustive, rather it provides a starting point):

- clinical research organization (CRO);
- clinical investigator(s) or treating physicians;
- individual patient advocates/influencers/bloggers/ambassadors;
- patient panels or Patient online communities.

2. Patient pools or networks/platforms

Patient pools or networks that are organized around public institutions may provide a good reference to patient experts who are already involved in research projects. For example, **the European Commission's Innovative Medicines Initiative has an expert patients pool**[18].

- Specific networks or platforms for patient communities might serve to identify some patients to participate. For example, FindMeCure's trial hub[19] and EUPATI[20] platforms offer means to connect with patients.
- Use the literature and past research to identify potential patient organization that have been involved with research before.
- Consider social media listening within the medical area to capture general insights and identify key opinion leaders or active patients and patient advocates.

1.3. Select and invite patients

Goal

The goal of this activity is to select a group of patients (from the pool of candidates) who represent

[17] Find more information about questions to ask in this patient survey is mentioned also in Book 1, section 2.2 Co-developing discussion questions with Patients (page 19). Direct link to the additional questions here.

[18] Innovative Medicines Initiative, 2019 (https://www.imi.europa.eu/get-involved/patients/imi-pool-patient-experts)

[19] Trialhub, 2020 (https://trialhub.findmecure.com/)

[20] European Patients Academy (EUPATI), 2020 (https://www.eupati.eu/)

the full spectrum of the condition. Patients who express an interest in a patient organization's outreach can be selected for participation based on criteria specific to the project.

Rationale

- Selecting patients who represent the spectrum of the disease optimizes the collection of relevant information.
- Selecting motivated patients will maximize chances of engagement and participation.
- Identifying patients who may be initially reluctant but could be motivated through education of their potential contribution.

Methods for selecting patients

The preclinical research team and patient organization should work together to select inclusion criteria and candidate suitability.

Considerations for the Research team

- Identify patients to be involved in a patient's panel, working with the patient organization where applicable.

Consideration for the patient organization

- Contact potential patient participants by any means of communication to which there is mutual agreement to conduct a short interview. The short interview aims to confirm the patient's interest, explain goals and expectations, establish transparency (for what will the research team use the information, why it is important to obtain patient input, ensure the patient would make a good candidate for project participation, etc.).

1.4. Help Patients learn about preclinical research

Rationale

The success of any meeting described in the course of this document depends on Patients' understanding of preclinical research. Because most people have no experience with, or knowledge of preclinical research, it is necessary that patients understand preclinical research so they can provide informed input into the work of the preclinical research team.

Goal

To provide patients with knowledge on preclinical research so they can understand the context and content of future discussions and contribute consequently during discussions. This gives Patients the opportunity to be meaningfully involved with research.

Methods and tools for implementing the educational activity

Research team hosts an informational session with Patients selected for the project. A webinar is one possible format, but this session should be done in whatever way suitable to the project and the Patients involved. **This is a crucial educational step to inform patients of the preclinical research and should not be skipped.**

Broad topics for the informational session

- Why is preclinical research conducted?
  - What are the goals of preclinical research?
  - Why do Pharma, government, and other entities recognize patient input as important in discovering and developing new medicines?
- How is preclinical research conducted?
  - How are preclinical research goals achieved?
  - Overview of steps and timing of preclinical research.
  - Discovery and basic research: targets, pathways, and mechanisms of action.
  - Overview of the condition-specific preclinical research (within the organization).
- When is preclinical research conducted?
  - Where in drug development does preclinical research fit?
- Who conducts preclinical research?
  - Provide details of who is involved in preclinical research and include information on the regulatory bodies that establish requirements, evaluate the robustness of the research designs and the meaning of the resulting data.
- Content to be gathered and how it will be used by research team.
-

See Annex 2 for additional information on preparations for interactions for both Patients and Researchers

Send pre-reads and material before the informational session and ensure that such material meets accessibility considerations.

For further information and tips regarding accessibility see Annex 1

Consider consulting with Medical Affairs, Public Affairs and other partners within the organization that have a significant understanding of how disease-state information is currently conveyed to this specific patient population.

It may also be necessary to provide materials at a number of cultural and competency levels to ensure full inclusion of the patient population sub-types; in this case, it may be helpful to set expectations in a cover communication as to what the specific goals of providing the pre-reads is, and that more materials are being provided than the participant may need to read to meet those goals.

1.5. Conducting the Patient-Researcher Exchange Meeting

Suggested attendees (10 panellists[21])

- the condition-specific preclinical research team (including toxicology/ pathology);
- clinical team representatives (optional; would provide context for transition from preclinical research to clinical research);
- Patients and caregivers (caregivers will enrich the discussion);
  - Number of patients/caregivers might be limited by the number of patients patient organizations can identify.

Structure of the meeting

The meeting can be divided into four sessions:

1. Introduction

Expectations are set and questions are taken before the start of the program.

2. Preclinical team presentations

The general research approaches, results, challenges, are presented, including (in-person or virtual) laboratory tours, etc.

Purpose: inform patients on the goals of preclinical research.

If a virtual format is used, virtual tours of laboratories and some procedures (e.g., assays) are highly recommended. However, even in an in-person setting a virtual laboratory tour is very informative if an in-person tour is not possible.

3. Testimonies by patient panelists

Patient testimonies inform the preclinical research team on the impact of the condition on patients' daily life and the frustrations or successes related to the treatments they take. Two patient panels are suggested:

- Patient Panel 1: Symptom burden; five minutes per panelist testimony;
- Patient Panel 2: Treatments or other therapeutic solutions: what treatments or therapeutic solutions exist, what patients take, what works, what does not, patients' aspirations for ideal treatment; five minutes per panelist testimony.

4. Moderated discussion with patient panelists

The Moderated Discussions is where most insights will be gained by both parties. These discussions are best held after each of the above sessions to discuss "front of mind" topics. During these sessions the moderator pursues points raised in presentations and testimonies, poses co-created questions, and addresses additional topics relevant to the preclinical research team. Posing pre-formulated polling questions after testimonies can aid in focusing the moderated discussion.

A discussion on patients' views, preferences on aspects of clinical trials, risk/benefit issues should be included.

[21] Following the meeting format of Externally-led Patient-Focused Drug Development meetings (U.S Food and Drug Administration, 2019)

2. Format options for meetings

Depending on the purpose of the engagement, the format of the activities may differ. Patient input can be gathered in various formats and forums and a range of formats may suit the project's needs. Particularly relevant for this stage of the drug development process and the need to establish relationships with patients are in-person meetings.

These allow for in-depth discussions on complex topics and provide a chance for a one-on-one dialogue as well as group conversations.

- **In person meetings**
  An in-person meeting might be the preferred format, as it maximizes the chances for establishing trust and collaborative relationships.
- **Virtual meetings**
  However, during certain situations such a forum poses health (e.g. during the current COVID-19 pandemic) or security risks to all stakeholders. Therefore, we recommend then using a virtual format (e.g., over Microsoft Teams, Zoom, etc.). A virtual approach can maximize the feasibility of diverse, worldwide stakeholders to participate, removes the expense of travelling and potential accommodation requirements, and could sometimes create more time for the forum with participants who will likely be less tired without a travel.

  The key for a successful and productive virtual meeting is to be clear about the type of event being created and the objectives to achieve. Then choose the virtual format and digital tools best suited to achieve these objectives. For certain virtual meetings, the patient organization can help prepare the Research team on how to present to non-scientists.

Consider with Patients the outcome expected and review the methods and more detailed instructions in the Annex 2.

Meetings using a moderator

The moderator must be prepared with a basic knowledge of the condition, an understanding of the patients' symptom burdens and their experiences with treatments.

This background can be obtained from the results of the patient survey conducted before the meeting, information from the patient organization, or from historical information from the project (records from previous meetings with patients).

The moderator must also understand the goals of the research project and what the research team seeks to achieve from the meeting with patients.

Formats of moderated discussion:

In formats below, the moderator guides the discussion by directly interacting with panelists (no chat box, no virtual hand raising)

- Patient panel: Patient panelists and moderator are displayed on screen.
- Research team: Scientists and moderator are displayed on screen.
- Mixed panel: Patient panelists, scientists, and moderator are displayed on screen.
  - This option permits direct interaction between patients and scientists.
- Remaining audience (e.g., research team, others) may raise hands virtually and be called on to give live comments or ask questions.

Other possible methods of gathering patient input in preclinical research include:

- Patient Advisory Boards;
- Community Advisory Boards (organized by the (patient) community, as opposed to Patient Advisory Boards which usually are organized by other stakeholders such as pharma or researchers);
- written feedback from patients;
- Patient steering committees;
- interviews;
- focus groups;
- surveys;
- online bulletin boards;
- Patient summit or research days.

3. Other considerations

Behavioural considerations

To ensure meaningful engagement from all partners, attention should be put on maintaining respectful and collaborative preparation for and during meetings. All participants need to:

- actively listen to each other;
- express empathy/ see the other's point of view;
- receive feedback and input with an open mind (without being defensive);
- there are no wrong answers.

Duration of meetings

The length of the meeting will depend on the tolerance of the patients and whether the format is virtual or in-person. For virtual meetings, we recommend single or sequential meetings of lengths mutually agreed upon by Researchers and Patients.

Possible lengths include a single-day meeting or two three/four-hour sessions over two days.

Tools to collect answers or aid the discussion:

- Polling application to add interactivity to the meeting by polling or for gathering feedback (e.g. PollEverywhere.com, Mentimeter.com).
- If possible and patients consent, record the meeting and create a transcript to provide a permanent record for use by the preclinical research and development teams during subsequent development stages of product(s) in this therapeutic area.
- If feasible and with consent, sharing patient input (de-identified and adhering to data protection regulations) with other research teams or companies might benefit both the research and patient community.
- A meeting report should be written and approved by both sides within a reasonable period of time (suggestion: 2 weeks).

Logistical considerations before meetings

Well-thought through considerations for accessibility before and during meetings are a way to ensure all participants feel their needs have been taken into account. In unclear situations, patients can be asked about preferences and needs.

This also helps build trust in the relationship. Some considerations have been listed in the Table 3 below that can also be used as a printout checklist. It might not be comprehensive but serves as a start that applies in many meeting situations.

Table 3. Checklist for meeting logistics and accessibility considerations

Considerations	Y/N	Notes
Accessibility		
Accommodate communication needs of those with mobility, hearing or language impairments/ difficulty allowing for suitable arrangements to be made to accommodate.		
Accommodate participants' schedules and offer to reschedule when they are unable to attend or offer alternative ways to be involved.		
The venue, rooms accessibility and agenda organization should be tailored for people with debilitating health conditions and disabilities that cause fatigue, reduced attention span and physical discomfort by offering frequent breaks.		
Prior to the meeting, put together team members' (the full project team and/or all contributors) headshots, biographies, and project roles and circulate on approval of each participant. » Draft a document to outline the roles and responsibilities of all team members.		
Circulate slides, and meeting minutes after team meetings in a timely fashion (pre-meeting materials should try to be circulated 2 weeks prior. Post-management minutes maximum 2 weeks after.).		

Time and accessibility need to be adjusted with regard to the patient's condition. Some Patients might experience fatigue, have visual impairment/other physical difficulties, and need extra time and potentially material in different formats and/or additional support. » If you do not know what the accessibility considerations are, connect with an appropriate patient organization or ask the contributing Patients upfront.	■	
Allow for sufficient onboarding process to ensure Patients are familiar with the proposed project and the aim.	■	
For material sent prior to meetings or interactions: » Allow enough time for patients to go through material or complete surveys that are required for in-person meetings. *For resources on writing in plain language and creating accessible services, go to Annex 1.	■	
Catering	■	
If food and beverages are provided, are they "condition friendly"? » Ask meeting participants about their dietary restrictions.	■	

The above recommendations for organizing the initial meeting are applicable to any further (and other types of) meetings and interaction formats with the patient community. Use the PEQG[22] as your reference when setting new partnerships and planning new projects with patients.

[22] PEQG - https://pemsuite.org/peqg/

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This How-to guide was co-developed with a large community of stakeholders (more than 45 individuals from 36 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, presenting it on multiple occasions and disseminating it even further than their own internal networks.

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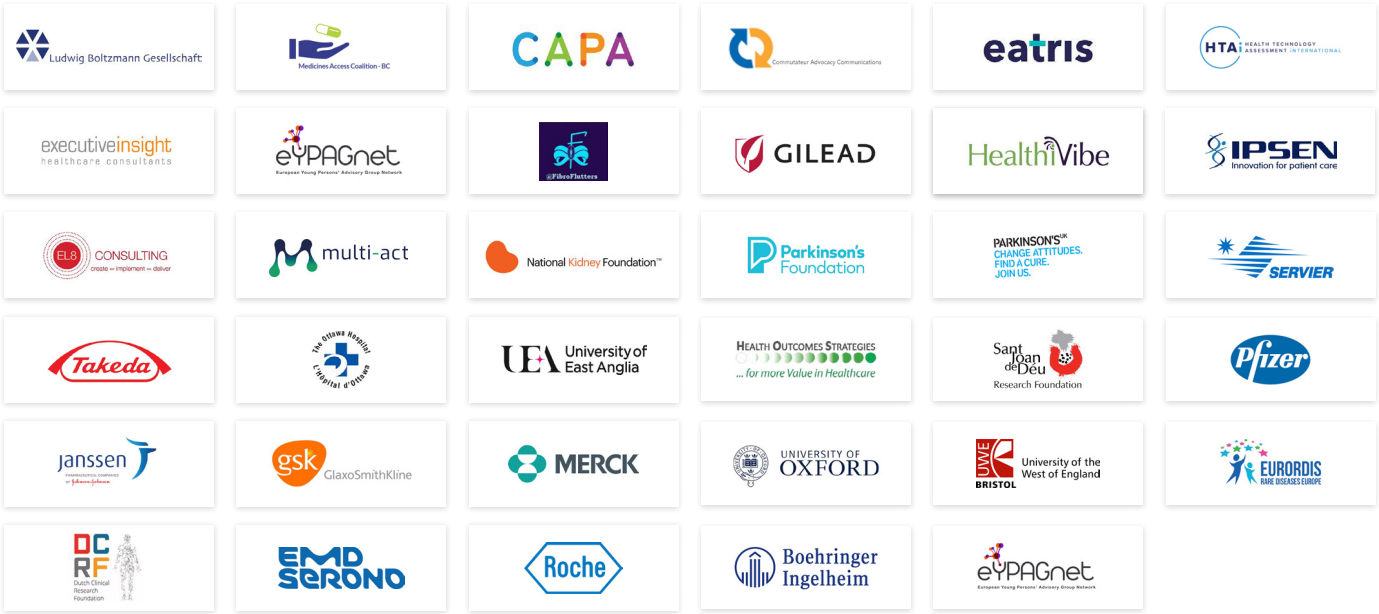
** Abbe Steel (Healthivibe), Angi Gillen (Gilead), Anke-Peggy Holtorf (Health Outcomes Strategies), Anne Charlotte (EATRIS), Begonya Nafria Escalera (Sant Joan de Deu), Berkeley Phillips (Pfizer), Casey Gallagher (Parkinson's Foundation), Daniel De Schryver (Janssen), Dawn Richards (Canadian Arthritis Patient Alliance and Clinical Trials Ontario), Deborah Bertorello (Multi-Act), Paola Zaratin(Multi-Act), Iraqi Wafae (Janssen), Jan Kulagowski (Parkison UK), Jeanette Ryan (GSK), Kelly Donlon Hoy (Merck), Lauryn Uribe (Gilead), Lode Dewulf(Servier), Paola Kruger (Patient Expert EUPATI Fellow), Paula Wray (University of Oxford), Richard Campbell (University of West England), Rie Kunisada (Takeda), Rob Camp (EURORDIS), Ronella Grootens (Dutch Clinical Research Foundation), Schiffon Wong (EMD Serono), Severine Wollenschneider (Roche), Thomas Schindler (Boehringer Ingelheim), Jennifer Preston(University of Liverpool), Kelli Collins (National Kidney Foundation), Manoj Lalu (Ottawa Hospital), Neil Bertelsen (HTAi), Ursula Davis (EL8 Consulting).*



Limitations and future possibilities

Patient engagement has gained traction within medicines development in the past years, but systematic involvement and engagement in the very early stages of discovery and preclinical seem to still be a novel idea with very limited experience. Within the community of PFMD Contributors, there have been very few specific guidances or frameworks identified that would have helped research teams to involve patients and for patients and caregivers to actively be involved early on.

We acknowledge that even with the collective knowledge of our working group we might not have been able to capture all frameworks and guidances that might exist for patient engagement in these early stages. This might mean that we have explained something that might have been covered in other tools already. However, we feel that this How-To guide serves as a comprehensive and self-standing set of instructions that can be used alone or even together with other guidances and have linked many in relevant sections. In terms of potential opportunities, many concepts and activities suggested for patient engagement within this How-To guide can be generalised and used in other phases or other health contexts when engaging the community.

The preparations for partnership and collaboration section can be encouraged to be universally used as it can be beneficial to other stakeholders to consider, not only those in the research stage. By properly preparing and focusing on setting up partnership instead of conducting a one-off event, all stakeholders will contribute to sustainable patient engagement practices.

We recognise the importance of scoping this How-to Guide into a concise package with enough information for anyone to start their patient engagement journey on the one hand, but also to not have an overwhelming encyclopedia that might deviate from the intention of making patient engagement easy to start, or discourage from it on the other. Because of the intention to maintain this balance, not all topics or additional resources were prioritised to be included. With this said, we see an opportunity to produce even more extensive instructions and considerations for all the topics and case studies. There is also an opportunity to take this work to the next level by providing "hands-on" support to adapt this into organization processes through training and other resources. This is something that PFMD will be exploring further. For any questions or ways to improve this How-to guide, please contact pfmd@thesynergist.org.

Annex 1
Preparations for setting up partnership and collaborations - Additional resources

The Patient Engagement Quality Criteria (PEQG[23]) was co-created to help all stakeholders set up partnerships and projects collaboratively. It can be used:

- when having first discussions with new partners to identify and align on shared purpose for the project, roles and responsibilities, accessibility considerations, feedback loop etc.;
- when assessing ongoing projects to see if there are aspects where you could improve to increase the level of engagement and participation;
- when retrospectively assessing completed projects to identify areas of improvement for future projects.

Access the Patient Engagement Quality Criteria checklists[24] to help plan and assess the level of patient engagement, criteria by criteria.

In addition to the checklists above to achieve each criteria, some additional tools that can also help achieve the 7 Quality Criteria, some of which are listed below:

For Quality Criteria 2 - Respect & accessibility

- Designing accessible service - a general guidance on how to design more accessible services. It covers best design practices for users from these areas: low vision, D/deaf and hard of hearing, dyslexia, motor disabilities, users on the autistic spectrum and users of screen readers[25].
- The INCLUDE Ethnicity Framework has four Key Questions, each of which is intended to prompt trial teams to think about who should be involved as participants, and how to facilitate their involvement as much as possible. These questions should be considered by Researchers in partnership with Patient and public partners.[26]
- Use plain language in all communications:
  - How to write in plain English[27]
  - Federal Plain Language Guidelines[28]
  - A PLS guide from MS Society[29]

[23] https://pemsuite.org/peqg/
[24] https://pemsuite.org/How-to-Guides/PEQG-Checklists.pdf
[25] https://ukhomeoffice.github.io/accessibility-posters/
[26] https://www.trialforge.org/trial-forge-centre/include/
[27] http://www.plainenglish.co.uk/How-to-write-in-plain-english
[28] https://www.plainlanguage.gov/guidelines/
[29] https://mssociety.ca/uploads/files/guide-to-writing-lay-summary-eng-final20130726.pdf

For Quality Criteria 3 - Representativeness of stakeholders

- PARADIGM Recommendations on how to find the right match for the right patient engagement activity[30]
- Global Site Network (ICON plc) - Feet on the ground: Access to hundreds of multi-speciality physicians[31]

For Quality Criteria 4 - Roles & responsibilities

- PARADIGM Code of conduct[32]
- PARADIGM Tools for the management of competing interests and conflicts of interest[33]

For Quality Criteria 5 - Capacity and capabilities for Patient Engagement

- PFMD Patient engagement training[34], which has been co-created with multi-stakeholder groups and shared for free. Levels 1 and 2 are suitable for all stakeholders, though geared towards build patient engagement capabilities for pharma
- PARADIGM Recommendations on required capabilities for patient engagement[35]

For Quality Criteria 6 - Transparency in communication and documentation

- PARADIGM Guidance for Reporting and Dissemination of Patient Engagement Activities[36]

Practical considerations

The importance of building a partnership

Build trust and a relationship with the patient community.

Get to know the community, join existing online community groups. Get to know people who run the groups, speak about your research or help demystify research and consider community engagement in social media. This not only improves Researchers' organization reputation within the community but also allows them to make connections that might help in the research. Use the 7 Quality Criteria and other similar frameworks to help set up partnerships and patient engagement projects.

Involve patients to plan outreach and the actual activity:

A person living with the condition can help identify the community and help in planning the activities (e.g. accessibility, representativeness, capacity considerations) so that Patients involved are equipped to meaningfully engage.

- Consider how the patient community can be supported to help in the research and how this can become a long-term partnership.

[30] http://imi-paradigm.eu/PEtoolbox/identification-of-patient-representatives

[31] https://iconplc.com/services/clinical-research-services/site-and-patient-recruitment/clinical-site-solutions/

[32] http://imi-paradigm.eu/PEtoolbox/code-of-conduct

[33] http://imi-paradigm.eu/PEtoolbox/conflict-of-interest

[34] http://learning.pfmd.org/

[35] http://imi-paradigm.eu/PEtoolbox/pe-capacity

[36] http://imi-paradigm.eu/petoolbox/reporting-and-dissemination/

- Try to get the patient organization to co-lead the outreach, co-organise the activity and co-facilitate.
- Think about how the result of your research will benefit the patient community.

Additional resources for setting up partnerships:

- For charities and patient organizations
  - Supporting patient and public involvement in industry-led research: guidance for charities[37]
  - Making a start: A toolkit for research charities to begin a PPI relationship[38] by Health Research Charities Ireland
- For researchers
  - Patient and Public Involvement & Engagement in Research - A "How-to" Guide for researchers[39]

Contractual matters

Collaboration between patients, researchers and other stakeholders should always be based on contracts that reflect the scope and purpose of the collaboration and is mutually respectful to all parties involved. Instead of using the company template, contracts should be adapted to fit the need of the project and unnecessary clauses should be taken off.

To help the community to collaborate, WECAN[40] and PFMD has collaborated to co-create with industry partners the guiding principles for reasonable agreements and 4 reference contracts for all stakeholders to use as a basis for to be adapted.

- Find out about the project and download the material from PFMD website or WECAN website
- Share the Patient engagement agreements explained[41] tool with patient partners.

  This co-created digital tool explains the reference contracts and the guiding principles further to allow the patient community to come to the table equally informed, even without a legal team's support.

Compensating patient and public partners

It is the responsibility of the researchers to start the conversation around compensation.

There are lots of guidelines to use for compensation, among which we mention:

- The **NHC's** Fair Market Value Calculator[42] and related tools
- **INVOLVE's** Involvement Cost Calculator[43] has a dummy project which can be used to test and calculate patient engagement project costs. This includes considerations for expenses as well as activity costs and payment for public and patient contributors for their effort. However, this

[37] http://slginvolvement.org.ukx/wp-content/uploads/2019/09/Supporting-PPI-in-industry-led-research_Guidance-for-Charities_CRIG-HRCI-public.pdf

[38] https://hrci.ie/a-new-ppi-toolkit/

[39] https://zenodo.org/record/3515811#.XIZ7YmhKiUm

[40] Workgroup of European Cancer Patient Advocacy Networks

[41] http://imi-paradigm.eu/PEtoolbox/contract-templates

[42] https://nationalhealthcouncil.org/patient-compensation-tools/

[43] https://www.invo.org.uk/resource-centre/payment-and-recognition-for-public-involvement/involvement-cost-calculator/

calculator does not suggest a fair market compensation for the public and patient contributors, but it gives a guidance and encourages to have a discussion with the public contributors.

- **CTTI's project "Realizing the Value of Effective Patient Group Engagement" (2018)** "To further support beneficial patient engagement, CTTI published a financial model that can be used to estimate the value of patient engagement on key business drivers such as cost, risk, revenue, and time—demonstrating that patient engagement can have a considerable impact on the bottom line."
  - Publication[44] and Findings[45]

The chosen guidelines should be presented to patient partners so they can understand where these numbers are coming from.

Patients do not need to accept the compensation.

Ask if they would be interested in accepting compensation and explain the income implications. Ask them if they have models they already use and consider adapting or using those models. Patients could also be interested in other types of compensation or reward for their participation, such as acknowledgement in papers.

Cultural adaptations to procedures

Practicalities such as meeting timing, location and format need to be adapted to the Patients' needs to allow increased participation and lower the burden of being engaged.

- A patient partner's lifestyle needs to be accommodated when scheduling and organizing meetings (i.e. work/ family schedule, ability to attend for long periods, etc.).
- If members are unable to attend meetings, offer to have a separate meeting to relay what was discussed at the team meeting. For in-person meetings, accomodation for individual needs is important.
- Give sufficient notice about planned meetings (a month in advance) and send out reminders.
- Circulate meeting minutes and next steps after each team meeting (recommendation: within 2 weeks).
- Consider the digital literacy of the patients. Consider scheduling a practice run with attendees that are unfamiliar with teleconference technology before the actual meeting.
- For more practical tips, see PFMD's collection of do's and don'ts[46] collected from the community and share your tips.

Check local regulations and common guidelines on how Researchers can work with the patient community. Here are a few sources to start with:

- ABPI Sourcebook for industry working with patients[47]
- EFPIA Code of Practice[48]

[44] https://journals.sagepub.com/doi/full/10.1177/2168479017716715

[45] https://www.ctti-clinicaltrials.org/sites/www.ctti-clinicaltrials.org/files/new_ctti_resource_26feb2020_final.pdf

[46] https://patientfocusedmedicine.org/practical-tips/

[47] https://www.abpi.org.uk/publications/working-with-patients-and-patient-organisations-a-sourcebook-for-industry/

[48] https://www.efpia.eu/relationships-code/the-efpia-code/

Annex 2
Understanding condition profile and therapy area
Additional resources

It is essential (for Researchers) to have underlying / basic knowledge of the condition from the start especially if the study is condition specific. This can be gathered from reputed condition related resources in libraries, or on the internet before reaching out to patients. The examples offered below are not meant to be exhaustive, but a starting point:

- There are community groups online and offline with whom it might be beneficial to build a relationship. When reaching out to the members in these groups, consider creating a short 3 question survey to help exclude the undiagnosed or self-diagnosed members (especially on Facebook groups) unless they are connected to a charity that vets its members.
- Consider a 'hackathon' type of activity at a focus group or support group gathering of patients (e.g. through any existing patient organizations) to generate as much information as possible.
- Consider creating a mixed stakeholder and long term Advisory Board that can advise or work alongside/ with Researchers throughout the project.

Additional resources mentioned in the text:

- Questions to understand the condition and therapy area[49] (from Book 1, section 2.2)
- Methods of Patient Engagement[50] (from Book 2, section 2)

Share and help Patients learn about preclinical research

If scientific publications are considered, be sure to choose those with plain language summaries. These are only a few examples to start with:

- Generic explanations of the medicines development process[51] from the FDA and the preclinical phase within it[52]
- Generic explanations of preclinical research[53]
- For explaining what patient engagement in research might look like:
  - EULAR Patient involvement in research- booklet[54]
  - Understanding what patient engagement is in research from INVOLVE[55]

[49] https://pemsuite.org/How-to-Guides/Questions-to-understand-the-condition-and-therapy-area.pdf

[50] https://pemsuite.org/How-to-Guides/Methods-of-patient-engagement.pdf

[51] https://www.fda.gov/patients/learn-about-drug-and-device-approvals/drug-development-process

[52] https://www.fda.gov/patients/drug-development-process/step-2-preclinical-research

[53] https://en.wikipedia.org/wiki/Preclinical_development

[54] https://www.eular.org/myUploadData/files/Reference_cards_explained_Booklet_pages_23-08-13_1.pdf

[55] https://www.invo.org.uk/find-out-more/what-is-public-involvement-in-research-2/

Priority setting - additional resources

Methods and best practice examples:

- Example for research question prioritization[56]
- Crowdsourcing research questions in Science e.g.: Tell us projects[57,58]
- Priority Setting Partnerships[59]
- Patient powered research networks[60]
- Patient-led research hub[61]
- Patient-led rapid prototyping[62]

[56] https://priorityresearch.ie/

[57] https://www.redensiemit.org/home-en.html

[58] https://tell-us.online/

[59] http://www.jla.nihr.ac.uk/

[60] See the section 2.1 https://www.tandfonline.com/doi/full/10.1517/17460441.2015.1037271

[61] https://plrh.org/

[62] https://patient-innovation.com/

Annex 3
Developing a research approach
Additional resources

Preparations

In preparation for developing a research approach, consider involving:

1. patients, caregivers, and family members with lived experience with the condition in question;
2. advocates and people who work in advocacy for this or a similar disease;
3. members of the public (i.e. the term citizen science).

These groups can bring different but valuable perspectives to the project and ideally, members of both groups would be engaged throughout the duration of the research project. Looking for existing groups (usually of patients or "mixed") is a good place to start.

Refer to the preparations section (in addition to the short list below) to prepare for activities related to development of research methods. After identifying the interested patient organizations or individual patients to partner with the Research team, it is pivotal that new members go through an onboarding process. Some examples follow to achieve effective onboarding:

- Suggest meeting one-on-one with the patient organization to go over the research project (background, rationale, aims, methods, and future directions).
- Introduce the concept of patient engagement and ask Patients where they want to contribute (if they have any preference) and suggest ways that Patients can contribute (as options).
- Schedule a future meeting to go over questions and comments about the project or terms of reference (after reviewing the resources provided) and to introduce Patients to each other.
- Clarify who Patients should contact (and how to contact them) on the Research team if they have any questions/comments/concerns. This team member would act as the point of contact for Patients.

Key activities

Priority setting in research with respect to granularity of the priorities; time point of the study (doesn't always have to be at the beginning) and facilitation of priority setting. Having physicians and Researchers discuss with Patients has been a highlighted importance, but there is also a need to involve methodologists and biostatisticians to discuss with patients the kind of measurement methods, and preferences/weighting of endpoints or results that are to be considered in the research.

How to incorporate patient engagement in early discovery studies (i.e. bench research)?

- **Priority setting:** ensuring that research priorities align with the downstream priorities of patients.
- **Governance:** overseeing the conduct of the project and providing feedback.
- **Education and advocacy:** discussing the project and purposes to educate patients or the public about scientific research as there exists a knowledge gap between what is being and the results translating to members of them in practice.

- Drafting grant applications/letters of support and manuscripts with Patients

The following additional examples of patient engagement in the preclinical stage illustrate the importance of why it should be done and how it is done by some organizations.

How to measure 'success' of the drug in the lab vs. in the clinic

It's important to think about how outcomes and the effects of the drug are measured at this stage of the research compared to how the effects of the drug will be measured when the drug moves into clinical trials. If a drug or compound shows promise, or is found to 'work', in lab-research, how will this translate into a meaningful clinical outcome?

How will the measure of success used in the lab translate to a measure of success in humans? For example, if a drug is shown to increase the number of dopamine neurons in an animal model, can the same thing be measured in humans? And what would we expect this increase in dopamine to look like for the person - e.g., expected change in motor symptoms?

Things in the lab are often measured in very fine detail, but then when it comes to the clinic, we do not have any way of measuring this in humans so we are relying on proxy measures such as questionnaires. It is important for researchers to consider whether they can introduce some other measures of 'success' in the lab so that findings might better translate in clinical trials.

Acceptable routes of administration and medication schedule

It is important to understand what route of administration people are happy with. The route of administration affects how a drug works, and how long it will last in the body. Chemical alterations may need to be made to extend the life of the drug to make it more practical for people to take. But then these alterations might have other consequences - would these be acceptable to people?

Developing a virtual patient profile for simulations and in silico initiatives:

In some studies (oncology, rare conditions, paediatrics, haematology etc.) comparisons with placebo (control) groups of patients are considered unethical, which has been more and more publicly scrutinized over the recent years. Developing virtual profiles of patients with the dedicated medical condition could be considered as a potential solution. To develop such profiles:

- Scientists should take as many as possible characteristics of people living with this condition by gathering insights on key symptoms/manifestations, complications and comorbidities, quality of life and others.
- Modern modelling technologies allow consolidation and qualitative validation of such characteristics creating an ordinary profile of patients to represent a control group.
  - Please, note that virtual research technologies and simulations are under regulatory review now, therefore there is not widely accepted/established practice yet.
  - Newly created profiles must be discussed and agreed by real patients and care partners.
- EXAMPLE: Video of Dr Heather Mortiboys discussing PPI in her lab-based research[63] and how she switched from using animal models to patient-derived cell models.

[63] https://www.youtube.com/watch?v=KTxQKngFIbs&feature=youtu.be

Pharmaceutical development - new delivery system developed with patients:

Over the last decades the well-known standard of care for several neuroendocrine conditions was to administer medicines through a syringe with a thick needle for deep intramuscular injection. Although using the product has demonstrated good efficacy outcomes, its delivery system has caused a lot of tolerability issues, mostly around the injection site (painful injections, swelling, irritation, redness etc.) as well as reported inconvenience for self-injection mode. The pharmaceutical development team decided to upgrade the delivery system for the product improving therapeutic compliance and patients' satisfaction.

A series of advice-seeking and insight-gathering activities were conducted with patients and care partners, so researchers collected the most desirable characteristics of a delivery system for the injectable medicine.

A new delivery system was co-created with an ergonomic, adjustable handle for self-injections, thinner and a sharper retractable needle. Patient experience has significantly improved, and such changes were accepted positively by the majority of patients.

Published evidence of patient engagement at the early research:

- Giving Voice to Patients: Developing a Discussion Method to Involve Patients in Translational Research[64]
- Future of Rare Diseases Research 2017–2027: An IRDiRC Perspective[65]
- Brief Report: A Survey of Autism Research Priorities Across a Diverse Community of Stakeholders[66]
- Transforming research: engaging patient advocates at all stages of cancer research[67]
- Participatory Genomic Research: Ethical Issues from the Bottom Up to the Top Down[68]

[64] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6267162/

[65] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5759721/

[66] https://pubmed.ncbi.nlm.nih.gov/29948533-brief-report-a-survey-of-autism-research-priorities-across-a-diverse-community-of-stakeholders/

[67] https://pubmed.ncbi.nlm.nih.gov/29911115/

[68] https://pubmed.ncbi.nlm.nih.gov/28426284/

Annex 4
Target Value and Target Product Profile
Additional resources

The Integrated Development Plan and Target Value Profile (as part of Target Product Profile)

The Research team creates an Integrated Development Plan(IDP)[69]. The IDP brings together the current cross-functional understanding and insights of the indication, including patient insights into how to plan to effectively bring a molecule through development and generate the right evidence to achieve marketing authorisation and market access at the end of R&D cycle. In essence, the TPP and TVP is 'what a researcher aims to achieve' and the IDP is 'how to achieve it'. An IDP and patient input to IDP are discussed under the section "Developing research methodology" in this document.

Taking the complexity of an IDP with many special terms and traditional research abbreviations, it is critical that researchers provide training and explanations in lay language to Patients prior to moving forward into a discussion. The critical decision-making milestones, such as whether the research will continue or ends (Go/Go or No/Go decisions), on further investment and respective business case update traditionally takes place upon such TPP reviews/updates.

For TVPs it is critical to remember:

- The TVP (as a part of TPP) should always reflect the medical indication for a specific molecule.
- The TVP comprehensively summarises all findings and insights gathered around the certain medical condition, therapeutic area profile and existing standards of care according to the latest guidelines, gap analysis and scientific methodology (see previous steps and sections).

How to create TVP attributes from TPP with Patients - a printable checklist

Each of the TPP elements are listed on the left column with characteristics explained in the middle column. On the right column are questions to Patients. Patients' insights help build the value proposition to the TPP, hence it is called the Target VALUE Profile.

Consider printing out this table to have a question list at hand to discuss with Patients.

[69] The TPP and IDP are highly confidential documents which are ideally updatable upon new data and findings available and reviewed by relevant scientific board and/or independent data review or monitoring committees (IDMC or equivalent)

TPP element	Examples of TPP characteristics	Questions to be validated with patients to inform TVP attributes (based on unmet patient needs)
Indication	• Medical condition(s): severity/activity of the process (mild/moderate/ severe, symptoms/manifestations and complications; other grades by widely accepted clinical classification; • Comorbidities/co-infections; • In Prevention, treatment or diagnosis; • In mono- or combined therapy; Alternatively, consider any other grades that are widely accepted in clinical classifications (rate of progression, etc).	• Which symptoms/manifestations patients suffer from most? • What should be managed first? • Which manifestations aren't managed by the existing standard of care (SoC)? • How well satisfied are patients with current treatments for the condition? • What condition would the medicine be used for? • If aiming for a symptomatic treatment across conditions, how does experience of that symptom vary across conditions? • Which other treatments/approaches might be combined with?
Target population	• By age (children, adult, elderly); • By gender; • Stage/experience living with a condition (e.g. people living with HIV: naïve, heavily treatment experienced, stable on treatment etc); • Special characteristics, except co-morbidities (smokers, drug users); • Consider also specific geographical areas. For example, people living with HIV: naïve, heavily treatment experienced, stable on treatment etc.	• Who would the medicine be for? • Will the treatment be focused on a specific subgroup? • Does this reflect their unmet need? • Could the scope be extended to cover a broader group? • How well managed are they by current therapies? • How well would this type of medication work for a specific type of patient? • How does new treatment address diversity and heterogeneity challenges? • How might new treatment impact lifestyle and habits (e.g., injections might be a trigger factor for injectable drug users)?

TPP element	Examples of TPP characteristics	Questions to be validated with patients to inform TVP attributes (based on unmet patient needs)
Efficacy and effectiveness	• Peak of action; • Duration of action; • Onset in comparison with the SoC (non-inferiority or superiority); • Sustainability/stability of action; • Number (%) of intent to treat population achieved the certain clinical/lab/instrumental or other criteria by [time]; • Survival (overall and progression-free in oncology); • Specificity (for diagnostic technologies); • Sensitivity (for diagnostic technologies); • Need for additional diagnostic test(s) prior to therapy initiation; • Immunogenicity (vaccines).	• Does it work effectively? • How quickly does it work? • How better/quicker/more effectively does it work in comparison with the existing treatment options? • What do patients expect from new treatment? (e.g. should work fast, with long-lasting effect, stability through the time) • What effect should the medicine have on the condition? • How often should treatment be given? • How would this medicine reduce a specific burden of living with this disease? • How is efficacy measured and is this approach meaningful to patients? • Consider survivorship • Related conditions and services to ensure highest efficacy of new treatment in targeted population and beyond • What are the associated treatments/ approaches to enhance efficacy (for example boosted combinations)?
Resistance (for antimicrobial agents)	• Barrier to resistance development; • Cross-resistance with other classes; • Cross-resistance within a class; • Impact on future treatment options if therapy fails; • Polymorphism; • Need for additional diagnostic test(s) prior to therapy initiation.	• How quickly could this medicine become ineffective? • How will taking this medicine impact the ability to take other medications in the future? • How will taking this medicine impact that ability of other people not yet infected with a specific microbe to get effective care? • See above "Efficacy and effectiveness".

TPP element	Examples of TPP characteristics	Questions to be validated with patients to inform TVP attributes (based on unmet patient needs)
Safety profile	• Specific safety signals should be easily manageable; • Non-inferior/superior safety profile in comparison of SoC; • Need for additional or unique monitoring prior to or during therapy; • Interactions with commonly co-administered medications; • Contraindications especially with common comorbidities; • Considerations for specific populations (e.g., pregnancy, lactation, children down to age 2 months, elderly); • Restrictions for women of childbearing potential. For example: pregnancy, lactation, children down to age 2 months, elderly. Restrictions for women of childbearing potential.	• What kind of possible side effects are there? • What kind of side effects of the existing therapy/SoC are the most critical? • What side effects would be acceptable to patients and what might change that decision? • What would be a meaningful improvement compared to current therapies? • How many adverse events are there? • Which side effects of the existing therapy/SoC are avoidable/ manageable? • What are acceptable risks/side effects for patients? (It's important to ask people and not presume.) • How would side effects affect adherence? • Will there be possible interactions with other medicines and what would be their consequences? • Are there special monitoring measures and ways to prevent side effects? A side effect might be tolerable for 3 weeks and another for 3 years. OR a side effect might be tolerable until there is an important life event.
Tolerability profile	• Non-inferior/superior tolerability profile in comparison of SoC (reported as PRO); • % of potential users adapting to tolerability issues within one round of use;	• What is the effect of a treatment's side effects on patient treatment continuation? • What would be a meaningful improvement compared to current therapies?

TPP element	Examples of TPP characteristics	Questions to be validated with patients to inform TVP attributes (based on unmet patient needs)
Tolerability profile	• % of discontinuation due to tolerability issues; • No irreversible tolerability issue (issue that does not resolve after discontinuation of drug).	• What are the expected tolerability issues of the proposed treatment? (Please, note: tolerability issues may be reported as relevant PRO measurements in clinical trials. At the stage of TVP development it's important to consider patients' expectations from tolerability profile) • What kind of PRO/PCO measurements and tools should be used reflecting tolerability profile in the forthcoming studies? • % of study participants who have accepted/adapted to possible tolerability issues? • % of study participants who have discontinued due to tolerability issues? • Any expected irreversible tolerability issues?

Clinical pharmacology	• Pharmacokinetic (PK) and Pharmacodynamic (PD) relationship enabling:
	  ○ Faster achievement of the therapeutic levels;
	  ○ Broader therapeutic index (with no impact from intrinsic factors such as body composition, gender, weight, and age);
	  ○ Optimal dosage and frequency of administration;
	  ○ Ability to initiate new therapy rapidly without PK "tail" from previous treatment;
	• Clinically significant drug-drug interactions requiring dosage adjustment or contraindication with commonly used concomitant medications;
		• What medicine do patients typically use to manage the effects of their condition (i.e. pain & digestive issues)?
		• What are some of the other comorbid conditions seen in significant sub-populations of patients with this disease and how might this treatment option impact the overall patient?
		• What is the mechanism of action?
		• Is it innovative technology or expansion/sophistication of the existing class?
		• Is it broad enough (difference between minimal therapeutic dosage and minimal toxic dosage)?
		• Is there a need for dose adjustments in terms of gender, age (adults) and body mass index (BMI)?

TPP element	Examples of TPP characteristics	Questions to be validated with patients to inform TVP attributes (based on unmet patient needs)
Clinical pharmacology	• Minimal dose adjustment or contraindication for mild to moderate common comorbid conditions; • No contraindications of use specific populations (e.g., pregnancy or breastfeeding, elderly).	• How can it be combined with other commonly prescribed medicines? • Is there a need for dose adjustments in terms of taking other therapies? • Is there a need for dose adjustments in terms of common comorbid condition? • Any potential contraindications in terms of taking other medications and living with other medical conditions? • Any potential contraindications for specific populations?
Dosage and administration (posology)	• Formulation/formulations; • Types of administration/delivery; • Injection site/sites; • Injection volume; • Dosing frequency; • Number of pills per dose; • Dosing timing; • Dosing with relation to food; • Dosing adjustments (see the factors above); • Pill size; • Coformularity - ability to be co-formulated into fixed dose combinations and/or single tablet/ injection regimens; • Other posology aspects for alternative formulations.	• What are the most/least desirable formulations for this treatment? • What are the most/least desirable ways of delivery for this treatment? • Ideally, how should the new medicine be administered (oral, subcutaneous, intravenous) and where (at home, doctor's office, hospital etc.)? • Any changes in terms of formulations/ ways of delivery vs existing SoC? • Desirable/acceptable injection sites; dosing frequency; number of pills per dose; size of pills; dosing time? • Relation to food and drinks? • Relation to daily activities: physical, mental, sexual, working/daily routine, childbearing/breastfeeding? • Dependence from HCPs/clinics or care partners in terms of administration/delivery? • Maximal volume of injection (more relevant for subcutaneous and intramuscular injections)?

TPP element	Examples of TPP characteristics	Questions to be validated with patients to inform TVP attributes (based on unmet patient needs)
Dosage and administration (posology)		• Suggestions for delivery system (implant, pump, needle, general design etc.)? • Suggestions for medical device parameters (note: there are specific requirements for every new device, which should be considered separately)? • What are the preferred tactics in case of missed dose? • Pharmaceutical combinations with other medicines (in one formulation, fixed dose combination)? • How does the route of administration affect the 'working time' of the medicine and its efficacy? • Other dosage and administration aspects to be considered by developers? • How would a different route of administration fit within the current clinical process? • What would be a meaningful improvement compared to current therapies?
Storage conditions	• Expected packaging; • Shelf life (period) and stability; • Impact of temperature; • Impact of humidity; • Impact of light.	• Do such storage requirements present any challenges to taking the medication by patients? • Any issues patients may face during travelling time/outside home? • How should the new medicine be stored? • What would be an improvement compared to current therapies?

TPP element	Examples of TPP characteristics	Questions to be validated with patients to inform TVP attributes (based on unmet patient needs)

Business rationale (business case – may/ may not be a part of TPP)	• Public health considerations:
	  ○ prevalence and morbidity;
	  ○ mortality;
	  ○ disability rate;
	  ○ epidemiology;
	  ○ social burden;
	  ○ economic burden;
	  ○ ethical considerations;
	  ○ healthcare settings, infrastructure and condition management.
	• Estimated investment;
	• Estimated time for development;
	• Cost of Goods (COGs) per daily dose;
	• Estimated time of commercial availability (target launch year);
	• Target market price;
	• Proposed access & reimbursement models;
	• Estimated profitability and return of investment (forecast).
		• Are there any other patient-relevant factors that should be considered for the molecule? (e.g. Is the healthcare system set up appropriately, or have the necessary infrastructure in place to effectively deliver the product to the patients that need it?
		• What cultural, social and ethical factors are applicable and should be accounted for?

Value proposition	There is a set of unique product characteristics from above which could demonstrate the value of potential treatment from several perspectives: patients', care partners', payors', HCPs', healthcare systems. If the programme is successful, those characteristics alongside the generated data inform the HTA submission. The TVP directly influences the value proposition.	There is a set of key values highlighted as answers to the questions above which comprehensively reflects a consolidated value to be delivered to patients through administration of the new treatment.

Annex 5
Glossary of terminology used in this How-To

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 (where applicable, the direct links have been added for ease of access to further information

Terminology	Explanation
A	
Adherence	In medicine, adherence describes the degree to which a patient correctly follows medical prescription. Equivalent to the term "Therapeutic compliance" used by healthcare professionals and academia. Poor adherence is often associated with patients not following prescribed medicines and treatment regimes. Non-adherence or poor adherence has been reported as a major problem in medical practice and can also affect the outcomes of a clinical trial. Poor adherence, or failure to follow treatment instructions, may be attributed to several reasons such as poor communication, forgetfulness, or unpleasant side-effects. Efforts to improve adherence in clinical practice have included simplifying medication packaging, providing medication reminders, improving patient education, and limiting the number of medications prescribed simultaneously. Various measures of adherence are used in clinical trials, for instance: the assessment of pharmacological response, electronic diaries, residual tablet count, devices to monitor tablet removal from containers, testing for medicine in blood etc. (EUPATI).
B	
Burden (of condition)	A difficult situation or several aspects of unpleasant responsibility that healthcare systems and several healthcare stakeholders must deal with or worry about the certain condition, condition or health care issue. The term is used in health technology assessments (HTAs) to evaluate individual (personal health and wellbeing) as well as institutional impact (economic/financial, social, legal, administrative/operational, human resources etc) of given condition/issue/condition. (Cambridge Dictionary).
C	
Condition (Medical condition)	Condition (medical condition) is the particular state that something or someone is in. Medical condition is a much broader term than living with a certain condition(s)/morbidity (-es) or comorbidities. It could include pre-/not diagnosed condition, risky or self-harmful behaviour, habits/addictions, abused use of medicines, drugs or alcohol, range of condition complications and disabilities as a consequence of a condition (but without any manifestations of an active condition), genetic/inherited conditions or abnormalities. Some physiology (normal) states may also be considered as medical conditions, for example, pregnancy, breastfeeding, neonatal period, ageing and others. Any medical condition, not just condition, may require medical monitoring and active management.

Terminology	Explanation
Condition profile	The set of characteristics likely to appear in a person living with a certain medical condition or conditions (see also "condition") including, but not limited to symptoms and manifestations.
Contraindications	A sign(s) (symptom(s), manifestation(s) that someone should not continue with a particular medicine or treatment because it is or might be harmful (Cambridge). In medical practice, contraindication opposes indication - medical condition for which a specific intervention (medicinal product, medical device, treatment, medical procedures) is developed to cure, relieve symptoms, prevent or diagnose. Both indications and contraindications are important sections of the 'Summary of Product Characteristics' (SmPC) document, which determines the boundaries of lawful use of such medicinal products.
Conformularity or co-formularity	An ability of several medicinal substances to be co-formulated (see also "Formulation") into fixed dose combinations and/or single tablet/injection regimens.
Cost of Goods (COGs) or Cost of Goods Sold (COGS)	Carrying value of goods sold during the particular period. In the case of medicines this value reflects costs of raw materials, synthesis, manufacturing, packaging, supply & distribution, operations, labour and allocated overhead (US the Financial Accounting Standards Board (FASB)).
Contract Research Organization (CRO)	CRO is an independent organization that provides support into the medicines' development process. Typically, a CRO organises and conducts clinical trials to test an investigational medicinal product in humans on behalf of sponsors (industry, academia or independent investigators). (EUPATI).
Clinical Research	Clinical research refers to all research carried out on humans (healthy or sick people). It focuses on improving knowledge of diseases, developing diagnostic methods and new treatments or medical devices to ensure better patient care. It is very framed and respects a precise study protocol and is only realized under certain conditions.Types of clinical research include clinical trials, which test new treatments for a disease, and natural history(observational) studies, which collect health information to understand how a disease develops and progresses over time. (FDA, 2018).
D	
Drug-Drug Interactions (DDI)	A change of a drug's (medicine's) effect on the body when the drug is taken together with a second drug. A drug-drug interaction can delay, decrease, or enhance absorption of either drug. This can decrease or increase the action of either of both drugs or cause adverse effects (U.S. Department of Health and Human Services (HHS), 2018).

Terminology	Explanation
Drug Development (in place of 'medicines' or 'vaccine')	For the purpose of this How-to Guide we choose to use medicines development to include vaccines and medical devices. Where applicable, the medicines or drugs that are still in the research and development phase - hence, not yet approved on the market. On some occasions, for the sake of fluency of the text, we use "medicines" because it fits the concept better. Medicines development comprises research and discovery, development (preclinical and clinical), marketing authorisation, post-approval, HTA, pricing and reimbursement, commercialization, lifecycle management and Pharmacovigilance until deregistration. (PARADIGM, adapted from: EUPATI; European Commission; EFPIA; Frontiers 'The Life Cycle of Health Technologies. Challenges and Ways Forward, Iñaki Gutiérrez-Ibarluzea et. al. 2017').
Delivery/ Delivery system	Medicine delivery systems encompass four main related aspects of delivery: 1) Routes of delivery (ways in which the medications can be taken, such as orally, by injection, by inhalation, etc.); 2) Delivery vehicles (dosage forms such as pills or slow-release granules); 3) Chemical/biological properties of the active substance of the medicine (the cargo); 4) Targeting strategies (delivery methods that deliver medicines to specific organs, tissues, tumours or structures inside of cells). Delivery device is a device used for the delivery of a medicine or therapeutic agent via a specific route of administration (e.g. inhaler, dermal patch or infusion pump). (EUPATI).
Disability (rate)	A prevalence of an illness, injury, or medical condition that makes it difficult for someone to do the things that other people do. (Cambridge Dictionary, n.d.).
E	
Early discovery, early research phase	In broader understanding, earlier phases of the medicines development continuum include all steps made before the first in human (FIH), or clinical research. Early research may include the following milestones: 1.Upon concept assessment prior lead identification (target identification, target selection and optimisation); 2.Upon lead optimisation prior candidate validation; 3.Upon candidate validation prior starting pre-clinical research (animal or human cells model); 4.Upon successful outputs of pre-clinical research (go-go decision) prior commitment to phase I clinical trial (first in human).
Efficacy	Efficacy refers to the ability of a medicine to provide a beneficial effect (a positive benefit/risk ratio) when studied in a clinical trial. When talking in terms of efficacy vs. effectiveness, effectiveness relates to how well a treatment works in the real-world practice of medicine, as opposed to efficacy, which measures how well a treatment works in clinical trials or laboratory studies. (EUPATI).
Effectiveness	The capability of a medicine to produce a desired or expected effect in the real-world clinical setting. When talking in terms of efficacy vs. effectiveness, effectiveness relates to how well a treatment works in the practice of medicine, as opposed to efficacy, which measures how well a treatment works in clinical trials or laboratory studies. (EUPATI).

Terminology	Explanation
Epidemiology	The scientific study of conditions and how they are found, spread, and controlled in groups of people. (Cambridge Dictionary).
F	
Formulation	A formulation is a mixture of different chemical substances prepared according to a specific method to create a medicinal product. (EUPATI).
G	
Gap analysis	A gap analysis is the process of identifying 'what is currently missing' so that it can be addressed. This can apply in terms of knowledge (e.g. understanding of patient burden) or a product (e.g. characteristics that the standard of care lacks). Gap analysis helps with suggesting some strategies/actions to achieve a desirable result using the certain resources (human, financial, data, operational etc.).
H	
Healthcare professional	The term 'Healthcare professionals' was used in this How-to Guide to include the following categories of occupations as defined by the International Standard Classification of Occupations: • medical Doctors – both Generalist and Specialist Practitioners, including Public Health Doctors; • nursing Professionals, including Public Health Nurses; • midwifery Professionals, including Public Health Midwives; • pharmacists; • dentists. Health professionals maintain health in humans through the application of the principles and procedures of evidence-based medicine and caring. Health professionals study, diagnose, treat and prevent human illness, injury and other physical and mental impairments in accordance with the needs of the populations they serve. They advise on or apply preventive and curative measures, and promote health with the ultimate goal of meeting the health needs and expectations of individuals and populations, and improving population health outcomes. They also conduct research and improve or develop concepts, theories and operational methods to advance evidence-based health care. (WHO, 2013).
HTA - Health Technology Assessment	Health technology assessment aims to inform decision making by health care policy makers. It is a systematic process that considers health technologies (such as medicines) and can involve a review of: clinical evidence compared to existing models of care, cost effectiveness, social and ethical impacts on the health care system and the lives of patients. The process advises whether a health technology should be used, and if so, how it is best used, and which patients are most likely to benefit from it.

Terminology	Explanation
HTA - Health Technology Assessment	Assessments vary, but most look at the health benefits and risks of using the technology. They can also look at costs and any other wider impacts that the technology may have on a population or on a society. They can also look at the relationship between costs and benefits and risks and make determinations about value for money. (EUPATI).
M	
Morbidity	The morbidity of a condition is how many people have it in a particular population. (Cambridge Dictionary.) Morbidity is based on two dimensions: incidence and prevalence. The Incidence of the condition is a number of new cases of the condition occurring within a specified period of time in a defined population. The prevalence of the condition is a number of cases of a condition that exist at a specified point in time in a defined population. Prevalence is of most use in determining the burden of chronic condition in the population and therefore is useful in allocating resources and planning healthcare services. (U.S. Department of Health and Human Services (HHS), 2018).
N	
Non-inferiority	A pre-study assumption/expectation or real result of a study when the one treatment/health technology has at least the same (non-inferior) efficacy and/or safety profile (or other characteristics) than the comparator (control). In such a case a conclusion about comparative profiles of two treatments/options may be made. Non-inferiority concept opposes the superiority concept when the one treatment/health technology has better efficacy and/or safety profile (or other characteristics) than the comparator (control).
P	
Patient advocate	In the context of this work, 'patient advocate' means patients who are doing the advocacy work of providing the voice of those who cannot do it for themselves, and who help to guide them through varying healthcare processes including research. (In general a patient advocate can also be a caregiver or a non-patient advocating for patients).
Patient organization (PO)	A patient organisation is defined as a not-for-profit organisation that is patient focused, where patients and/or care partners (the latter when patients are unable to represent themselves) represent a majority of members in governing bodies. (European Medicines Agency (EMA), 2014).
Patient Engagement	Patient engagement (in place of Patient involvement) There is no common language to describe a patient's involvement in the research and medicines development continuum and care journey. In this document, the term 'patient engagement' refers to the active and meaningful involvement of Patients in developing medicines. The following definitions should help to explain what we mean.

Terminology	Explanation
Patient Engagement	"Patient engagement occurs when patients meaningfully and actively collaborate in the governance, priority setting, and conduct of research, as well as in summarizing, distributing, sharing, and applying its resulting knowledge." (Canadian Institutes of Health Research, (2014). "INVOLVE defines public involvement in research as research being carried out 'with' or 'by' members of the public rather than 'to', 'about' or 'for' them." (INVOLVE, 2017) Patient engagement in NOT simply informing patients, surveying patients, consulting patients or having patients participate in research. It means working WITH patients.
Patient Input	Information that captures patients' experiences, perspectives, needs, and priorities"(FDA).
Patient Engagement Quality Guidance (PEQG)	Patient Engagement Quality Guidance is a co-created tool that contains seven measures to assess projects to involve patients.The PEQG is used to capture the quality of patient engagement projects and the benefits it brings to the stakeholders involved. This tool can be found on here. (PFMD, 2018).
Patient group	See Patient organization.
Patient-Researcher Exchange meeting	The Patient-Researcher Exchange meeting is the first (team) meeting that aims to educate Researchers and Patients and create a collaborative relationship. This Patient-Researcher collaboration should be dynamic and continuous, not a one-off event. The Patient-Researcher Exchange Meeting offers Researchers an opportunity to gather patient input.
Preclinical research (PRE)	Preclinical research is a stage/ milestone of the early research phase (see definition above) and includes several studies of a medicine candidate using human cell cultures or animal models. It may also be called "Translational research" or DMPK – Drug Metabolism and Pharmacokinetic research to evaluate candidate's cell/tissue metabolism (absorption, distribution, metabolism, and excretion of the medicine (ADME), non-clinical safety, toxicities and other critical parameters before moving forward to human. After this step called "Preclinical research", researchers review their findings and decide whether the drug should be tested in people, the next step called "Clinical research" which refers to studies, or trials, that are done in people. (FDA, 2018).
Preclinical teams (PCT)	Preclinical teams – teams of researchers, usually scientists with several life science qualifications (biologists, immunologists, biochemists, biophysicists, chemists, toxicologists, microbiologists, pathologists and others) responsible for conducting pre-clinical research. (FDA, 2018).

Terminology	Explanation
Posology	The branch of pharmacology and therapeutics concerned with dosage. (EUPATI).
Pharmacokinetics (PK)	Pharmacokinetics is the study of what the body does to medicine. It studies the absorption, distribution, metabolism, and excretion of the medicine (ADME), as well as bioavailability. These pharmacokinetic processes, often referred to as ADME, determine concentration of the medicine in the body, and the onset, duration, and intensity of a medicine's effect. (EUPATI).
Pharmacody-namics (PD)	Pharmacodynamics is the branch of pharmacology that studies what the medicine does to the body. Pharmacodynamics looks at the biological and physiological effects of a medicine, and their mechanisms of action at organ and cellular level. (EUPATI).
Prevalence	A dimension of morbidity, which is a number of cases of a condition that exist at a specified point in time in a defined population. (U.S. Department of Health and Human Services (HHS), 2018).
Patient Reported Outcomes (PRO) and Patient Centered Outcomes (PCO)	Patient Reported Outcomes (PROs) are data reported directly by a patient on his or her own health condition, without interpretation by a doctor or anyone else. They are based on a patient's perception of a condition and its treatment. The findings or outcomes can be measured in absolute terms (e.g. severity of a symptom, sign, or state of a condition or condition) or as a change from a previous measure. Patient-reported outcome measures (PROMs) are the tools used to measure and collect data on PROs. Generally, findings are measured by a well-defined and reliable patient-reported outcome (PRO) instrument. The use of a PRO instrument is advised when measuring an aspect of the condition or condition that is best known by the patient or is best measured from the patient perspective. By the contrast, Patient Centered Outcomes may not be interpreted by a patient only, but also by care partners, healthcare professionals and other healthcare stakeholders. The separate set of PCOs relate to the service delivery and satisfaction with the healthcare infrastructure settings. (FDA, 2009).
R	
Research and Development (R&D)	Research and development is a common title of the process of the medicines development (for pharmaceutical companies, academic institutions and other healthcare organizations) or respective function within those organisations responsible for medicines development starting from fundamental research to medicines' authorisation.

Terminology	Explanation
Return of Investment (ROI)	A performance measure used to evaluate the efficiency of an investment or compare the efficiency of a number of different investments. ROI tries to directly measure the amount of return of a particular investment, relative to the investment's cost. To calculate ROI the benefit (or return) of an investment is divided by the cost of the investment. The result is expressed as a percentage or a ratio. (Investopedia, 2020).
S	
Social media listening (or social listening)	A relatively new technology of insight gathering aimed to comprehensively monitor several social media resources with the focus on specific content (words, phrases, expressions, references etc.) related to the dedicated topic. The specific methodology and software are in use for social listening which allow to sort out everything relevant to the topic and conduct the content-analysis. Social listening could potentially be very helpful for gathering patient insights. Some best practice examples include social listening with the aim to detect any hidden safety signals (adverse events) not reported by patients to healthcare professionals, patient feedback on newly implemented treatments etc.
Sensitivity	Sensitivity (of an assay or test) is the ability of an experiment or trial to detect a difference – for instance, between two groups of participants receiving different medicines in a clinical trial. (EUPATI).
Signal (safety)	A sign/manifestation that shows that an adverse reaction is taking place or is likely to happen. Such manifestations may be clinically visible or detected instrumentally/ through detection of laboratory abnormalities (signal detection). Safety monitoring and risk evaluation systems/pharmacovigilance explore complex approaches to detect all possible safety-related signals either reported by patients/doctors or not.
Superiority	A pre-study assumption/expectation or real result of a study when the one treatment/health technology has better efficacy and/or safety profile (or other characteristics) than the comparator (control).
Stability	Stability is the ability of a substance to remain unchanged. Changes may occur due to the environment that the substance is in, e.g. being exposed to sunlight or water, or being in the body. Changes may also occur due to chemical and biological processes found inside the substance. (EUPATI).
Standard of care (SoC)	Treatment that experts agree is appropriate, accepted, and widely used for a given disease or condition. (U.S. Department of Health and Human Services. (HHS), 2018).

Terminology	Explanation
Specificity	Specificity (of an assay or test) is the ability of an experiment or trial to correctly detect only the particular effect being studied – for instance, a difference in symptoms between two groups of participants receiving different medicines in a clinical trial. If a trial is not specific enough, it will give a false positive result (Type I error). (EUPATI).
T	
Target Value Profile (TVP)	Target value profile (TVP) is a consolidated set of "expected and minimally acceptable characteristics" of a medicinal asset, biological product or medical device, which are valuable and meaningful for patients by addressing areas of remaining unmet needs. Alongside business rationale, public health factors and other elements for decision making, TVP informs the target product profile.
Target Product Profile (TPP)	(TPP) – an updatable guidance for the industry/developers with targeted characteristics of a potential product which based on real value for patients and other healthcare stakeholders (HCPs, care partners, payors etc.), business rationale, substantiation for investment, public health/environmental factors and other elements for decision making throughout the development continuum and product lifecycle.
Therapeutic area profile	Therapeutic area profile is a consolidated profile of existing treatment options under the standard of care (SoC) for the dedicated medical condition. Traditionally such options are presented by international/national clinical guidelines and protocols.
Therapeutic index or ratio	A ratio that compares the blood concentration at which a drug becomes toxic and the concentration at which the drug is effective. The larger the therapeutic index (TI), the safer the drug is. (U.S. Department of Health and Human Services (HHS), 2018).
Tolerability	The tolerability of the medicinal product represents the degree to which adverse effects can be 'tolerated' or accepted by a patient. Tolerability could be considered as a safety equivalent addressed by the respective patient-reported outcome measurements. (PROM).

References for the terms presented in this glossary can be found in the following resources:

- Cambridge dictionary
  https://dictionary.cambridge.org/
- CIHR Jargon Buster (Canada)
  https://cihr-irsc.gc.ca/e/48952.html
- Encyclopedic companion to medical statistics. Ed B.S Everitt and C.R Palmer/Second Edition, 2011.
- European Patients Academy for Therapeutic Innovation (EUPATI)
  https://www.eupati.eu/glossary/
- The RxNet Glossary of Drug Discovery
  https://www.future-science.com/doi/pdf/10.4155/fdd-2019-0101s
- Plain English Lexicon. A guide to whether your words will be understood/ Second Edition; 2011. Martin Cutts.
  https://www.clearest.co.uk/plain-english-lexicon
- NCI glossary (US) (of cancer terms, but many are also applicable to other areas)
  https://www.cancer.gov/publications/dictionaries/cancer-terms
- UC Berkeley
  https://undsci.berkeley.edu/glossary/glossary.php
- US Food and Drug Administration (The FDA)
  - Early discovery
    https://www.fda.gov/patients/drug-development-process/step-1-discovery-and-development
  - and preclinical research
    https://www.fda.gov/patients/drug-development-process/step-2-preclinical-research)

Annex 6
More resources and tools for patient engagement

PFMD Patient Engagement Management Suite (PEM Suite) for managing your patient engagement initiatives

Although already mentioned in the above sections, we want to highlight that the PFMD PEM Suite is a continuously growing suite of patient engagement tools to help all stakeholders to manage their patient engagement activities from setting up partnership, to How-To guides (yes, this guide will also be integrated there), patient engagement e-learning courses and more. It can bring value to your patient engagement activities and we recommend that you save the link, explore and revisit often to explore tool updates and new integrations.

- Explore all resources and tools in the PEM Suite from PEM Suite[70] and check back for new tools becoming available continuously.

PFMD Synapse Mapping and Networking tool[71] is a patient engagement hub that maps related resources, events, initiatives and showcases the network of experts and organisations relevant in patient engagement. Explore more from synapse.pfmd.org and create your account to unlock functionalities that can help you start and manage your patient engagement journey.

On Synapse you can:

- Search for relevant resources, tools and frameworks shared by other organisations through the Initiatives or Resources functions.
- Search and check out the patient engagement global network through People or Organisations functions.
- Learn about Conditions or search for condition related scientific publications or clinical trials.
- Create your organisation and invite your colleagues to start knowledge sharing internally or publicly to help make systematic patient engagement happen.

PARADIGM Patient Engagement tools[72] which has been co-created within the umbrella of Innovative Medicines Initiatives partnership. The set of tools, which PFMD has also been part of, presents a "PE Toolbox" that hosts 10 tools or guidances.

MULTI-ACT[73] is an EU-funded project that aims to increase the positive impact of health research on people living with brain disorders.The MULTI-ACT project works with patients and patient organizations, academics, private and public stakeholders to develop innovative tools to assess the value of research.

[70] http://www.pemsuite.org

[71] https://synapse.pfmd.org/

[72] https://imi-paradigm.eu/petoolbox/

[73] https://www.multiact.eu/project-deliverables/

Intercultural communication resources

- Culture Clues[74] are tip sheets for clinicians. They are designed to increase awareness about concepts and preferences of patients from the diverse cultures served by University of Washington.
- Intercultural Communication in Health Care[75]
- Health Literacy Universal Precautions Toolkit, Tool 10-Consider Culture, Customs, and Beliefs[76]
- Intercultural communication through the eyes of patients: experiences and preferences[77]

[74] http://depts.washington.edu/pfes/CultureClues.htm

[75] https://kkrum00.pressbooks.com/chapter/ch-13-health-care/

[76] https://www.ahrq.gov/health-literacy/improve/precautions/tool10.html

[77] Access at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5457791/

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