



Maximizing Patient Input in the Design and Development of Medical Device Clinical Trials¹

A Report of the Science of Patient Input Program
of the Medical Device Innovation Consortium (MDIC)

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¹The 21 CFR part 812 uses the term clinical investigations.
For purposes of the MDIC project, we use "clinical trials."

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About the Medical Device Innovation Consortium

The Medical Device Innovation Consortium (MDIC) is the first public-private partnership created to advance the medical device regulatory process for patient benefit.

MDIC was formed in 2012 to bring the U.S. Food and Drug Administration (FDA) and industry together to share vital knowledge that can help bring safe and effective devices in a cost-efficient manner to patients and providers more quickly. MDIC membership and participation is open to nonprofit, industry, and government organizations that are substantially involved in medical device research, development, treatment, or education; or in the promotion of public health; or that have expertise or interest in regulatory science.

MDIC is designed to pursue several strategies that support its mission:

- Create a forum for collaboration and dialogue
- Make strategic investments in regulatory science, utilizing working groups to identify and prioritize key issues, and to request, evaluate, and implement project proposals
- Provide and enable implementation of tools from these projects that drive cost-effective innovation

The activities and outputs from MDIC are intended to:

- Ensure that innovative technology is readily available to U.S. patients
- Provide industry and government with methods and tools that may be used to expedite medical device development and the regulatory process
- Reduce the risk and expense of clinical research
- Reduce time and cost of medical device development

MDIC members provide guidance and leadership through collaboration to develop solutions for regulatory, scientific, health, and economic challenges within the medical device and diagnostic industry.

MDIC Science of Patient Input Program

MDIC's Science of Patient Input (SPI) program provides a venue for continued collaboration to advance the art and science of patient engagement in regulatory science, including advances in methodologies and tactical considerations for integrating the patient's perspective and preferences in the design, clinical development, and regulatory review of innovative medical technologies.

Executive Summary

There are key distinctions between device trials and drug trials that present unique opportunities, challenges, and resource needs for engaging patient insights in the device field. In developing this report, the Science of Patient Input (SPI) Participation in Clinical Trials Working Group of the Medical Device Innovation Consortium evaluated a series of device trial characteristics (level of invasiveness, outcomes assessment, trial enrollment, and trial design) and prioritized them based upon their relevance for patient engagement.

A key step for sponsors seeking to pursue this work is to assess the reasons for doing it, when to do it, and how the input will be used. The report delves into the opportunities that exist for patient input to help define unmet need, clarify patient preferences, develop endpoints that measure what matters to patients, assist in reducing burdensome study protocol requirements to enhance recruitment and retention, and establish information that can be used in the regulatory process and for postmarketing activities.

Once the reasons for this work are clearly defined, the report provides information and resources that can be used to assist in evaluating and building needed organizational capacity to successfully pursue patient engagement in clinical development. This includes ensuring that this effort has appropriate internal leadership backing and sufficient resourcing (including training and appropriate legal/compliance input).

Patient engagement in clinical research is best viewed as a continuum that occurs in different ways, for different purposes, across the lifecycle of the product development path. A good rule of thumb to guide this work is “engage early and engage often.” Although the details of each engagement plan (with whom, when, how, etc.) will be tailored to the specific development and clinical research program, there are multiple baseline tactics that can be evaluated along the way. The report reviews a set of elements that can be incorporated into a sponsor’s patient engagement plan.

The report underscores that, when done correctly, patient engagement in medical product development is neither superficial nor episodic. The most successful efforts to leverage patient insights are those that recognize the value of this work and have embedded it into the corporate culture. Ideally, this commitment to patient engagement is held by company leaders and incentivized throughout the workforce.

Knowing which type of patient voice is most relevant to a development program can be challenging and is certainly not an “exact science.” Product developers seeking patient input should be aware of the variations in patient experience and related input and aim to evaluate the extent to which the insights they receive are representative for the population under study. The report provides a series of resources to help identify the most appropriate people to provide the “patient voice.”

Successful engagement with patients within clinical development requires a clear definition of what the patient’s role will be, from providing them a proactive, governance-type of “seat at the table” with the study team, to engaging them as advisors, to offering a more reactive role. The report addresses this topic and provides resources for sponsors to help define what is the most appropriate role.

The report encourages sponsors to take the time and make the effort to build relationships with patient groups and individual patients that are based on shared commitment to the effort, clear expectations, regular communications, and a common language about the project. Avoiding the perception that engagement activities are tokenism and are just being done to “check a box” by ensuring that all parties feel respected and able to contribute within the process is a key component of making this process meaningful. The report offers resources



to help sponsors with building the kind of trusting relationships needed to succeed. Included in this section are implementing a contracting and compliance process that is workable, providing appropriate compensation based on fair market value, and ensuring there is transparency and regular communication about the conduct of the study and how patients' input is being incorporated into the program.

It is hoped that this report provides a concise set of considerations for medical device developers to evaluate as they pursue patient engagement in their clinical trials and product development activities. Recognizing that this work is complex and made increasingly so by the heterogeneity of the device development landscape and understanding that no single compilation of information can provide everything a sponsor would need, the resources presented within this report are offered as a foundation from which sponsors can advance their efforts to generate and incorporate patient input into trial design and conduct.

As the field of patient engagement in clinical studies for devices evolves and expands, additional efforts could be undertaken by a variety of stakeholders to support sponsors, including:

- Development of device company trainings
- Development of case studies of successful activities in device trials
- Pursuit of projects to capture learnings and measure impact for the field
- Conduct of a follow-up survey of device manufacturers to compare with baseline results from the 2018 survey

Overview of the Report

This report is organized into the following sections:

Section One: Background and Objectives

Section Two: MDIC Framework Initiative

Section Three: Report Scope and Context

Section Four: Unique Device Trial Aspects

Section Five: Key Topics Overview

Section Six: Considerations for Device Developers

Section Seven: Opportunities for Future Work

SECTION 1

Background and Objectives

Developing patient-centered medical product trials has the potential to improve the patient experience in clinical trials, accelerate accrual, improve retention, improve data quality, and assure that the trials themselves are focused on outcomes that matter most to patients. All of this facilitates the development of innovative medical products that will make a direct and meaningful impact on the lives of patients.

The art and science of patient engagement in medical product development has evolved and expanded in recent years, in large part due to leadership from the U.S. Food and Drug Administration (FDA),² sophisticated patient advocacy organizations, and the work of organizations like Clinical Trials Transformation Initiative (CTTI),³ Patient-Centered Outcomes Research Institute (PCORI),⁴ Drug Information Agency (DIA),⁵ and the National Health Council (NHC).^{6,7,8}

FDA's work in this area has spanned 30 years, beginning with its efforts to engage patient input during the HIV/AIDS crisis in the late 1980s. Today, FDA's Centers, Offices, and Divisions have many complementary programs designed to incorporate patient insights into its regulatory activities.

There has been significant activity within the last decade in advancing patient-focused drug development (PFDD). As described by the FDA's Center for Drug Evaluation and Review (CDER), "[P]atient-focused drug development (PFDD) is a systematic approach to help ensure that patients' experiences, perspectives, needs, and priorities are captured and meaningfully incorporated into drug development and evaluation. As experts in what it is like to live with their condition, patients are uniquely positioned to inform the understanding of the therapeutic context for drug development and evaluation." In advancing its PFDD initiative, CDER has conducted meetings in more than 20 different disease areas to solicit and engage patient input for use in evaluating new therapies.⁹

² *Learn About FDA Patient Engagement*. U.S. Food and Drug Administration. September 11, 2020. Accessed February 11, 2021. <https://www.fda.gov/patients/learn-about-fda-patient-engagement>

³ *Patient Group Engagement*. Clinical Trials Transformation Initiative. Accessed February 11, 2021. <https://www.ctti-clinicaltrials.org/projects/patient-groups-clinical-trials>

⁴ Forsythe L, Heckert A, Margolis MK, Schrandt S, Frank L. Methods and impact of engagement in research, from theory to practice and back again: early findings from the Patient-Centered Outcomes Research Institute. *Qual Life Res.* 2017;27(1):17-31.

⁵ *Patient Engagement*. Drug Information Agency. Accessed February 11, 2021. <https://www.diaglobal.org/en/resources/areas-of-interest/patient-engagement>

⁶ *Integrating the Patient into the Drug Development Process: Developing FDA Guidance*. National Health Council, Genetic Alliance. May 4, 2016. Accessed February 11, 2021. <http://www.nationalhealthcouncil.org/sites/default/files/NHC-GA-Patient-Engagement.pdf>

⁷ *Dialogue/Advancing Meaningful Patient Engagement in Research, Development, and Review of Drugs*. National Health Council, Genetic Alliance. September 22, 2015. Accessed February 11, 2021. <http://www.nationalhealthcouncil.org/sites/default/files/PatientEngagement-WhitePaper.pdf>

⁸ *Patient-Focused Drug Development – Recommended Language for Use in Guidance Document Development*. National Health Council, Genetic Alliance. February 2017. Accessed August 14, 2019. <https://nationalhealthcouncil.org/wp-content/uploads/2019/12/NHC-GA%20Feb2017.pdf>

⁹ *FDA-Led Patient-Focused Drug Development (PFDD) Public Meetings*. U.S. Food and Drug Administration. November 24, 2020. Accessed February 11, 2021. <https://www.fda.gov/industry/prescription-drug-user-fee-amendments/fda-led-patient-focused-drug-development-pfdd-public-meetings>



The Center for Devices and Radiological Health (CDRH) has prioritized patient engagement through multiple activities, including establishment of its Patient Engagement Advisory Committee (PEAC) and issuance of a new draft Guidance on this topic.^{10,11} FDA leadership has encouraged medical device companies to include patient perspectives across the medical device lifecycle, writing in 2017 that “[A]dvancements in the science of patient input are needed to help ensure that clinical trials are designed to assess what matters most to patients and to facilitate patient enrollment in studies.”¹²

As device manufacturers pursue patient engagement activities, more specific information on how best to engage patients to collect and employ patient perspectives across the medical device lifecycle is needed.

¹⁰ Patient Engagement Advisory Committee. U.S. Food and Drug Administration. October 13, 2020. Accessed February 11, 2021. <https://www.fda.gov/advisory-committees/committees-and-meeting-materials/patient-engagement-advisory-committee>

¹¹ Patient Engagement in the Design and Conduct of Medical Device Clinical Investigations: Draft Guidance for Industry, Food and Drug Administration Staff, and Other Stakeholders. U.S. Food and Drug Administration. September 24, 2019. Accessed February 22, 2021. <https://www.fda.gov/media/130917/download>

¹² Faris O, Shuren J. An FDA viewpoint on unique considerations for medical device trials. *N Engl J Med.* 2017;376:1350-1357.

SECTION 2

MDIC Framework Initiative

In response to this need and building upon its pioneering work to advance the use of patient preference information in device development,¹³ the Medical Device Innovation Consortium (MDIC) is developing a “Framework for Patient Input in Medical Device Clinical Trials” (Framework). With an emphasis on evidence-based tools for engaging with patients, this project is focused on describing methods to integrate patient input into the design of clinical trials, advancing a transformative method for integrating patient preferences into the design of clinical trials, and synthesizing practical considerations for reducing the patient burden of participation in clinical trials.

MDIC’s approach in developing its Framework has been to research, examine, highlight, and synthesize existing work in these areas. Where possible, this effort has focused on tailoring existing resources for the specific needs of medical device clinical trials. Where there are gaps in existing resources, this initiative has refined existing approaches. The Framework provides a compilation of learnings from the overall medical product development field (including drugs, biologics, and devices), practical suggestions for undertaking patient engagement in clinical development, and considerations for determining when it is most important to engage patient insights.

The MDIC Framework effort comprises three subprojects:

1. Guidelines to integrate patient preferences into the design of clinical trials
2. Methodologies to maximize patient participation in clinical trials
3. A framework website reflecting all documents and resources created under the Broad Agency Agreement (BAA) that funded the effort

This report is focused on **Subproject 2: Methodologies to Maximize Patient Participation in Medical Device Clinical Trials**, whose deliverables include:

1. Literature review on existing efforts to reduce patient burden of participating in clinical trials¹⁴
2. Patient survey to elicit patients’ perspectives on the barriers to participation in clinical trials
3. Industry, advocacy organization, and healthcare provider survey to elicit perspectives on the barriers stakeholders face in partnering with patients for the purpose of eliciting patient perspectives on medical device clinical trial design and other operational aspects related to patient participation¹⁵
4. Review of successful practices developed by other organizations and assessment of their applicability to device trials (**addressed in this report**)
5. Summary of services and tools that have successfully reduced patient burden in clinical trials (**addressed in this report**)
6. Guideline document that synthesizes the findings of this project with actionable recommendations and a toolkit for maximizing patient participation (**addressed in this report**)

¹³ *Patient Centered Benefit-Risk (PCBR) Framework*. Medical Device Innovation Consortium. October 25, 2019. Accessed February 11, 2021. <https://mdic.org/resource/patient-centered-benefit-risk-pcbr-framework/>

¹⁴ *Literature Review: Patient Engagement in Clinical Trials*. Medical Device Innovation Consortium. October 25, 2019. Accessed February 11, 2021. <https://mdic.org/resource/literature-review-patient-engagement/>

¹⁵ *Patient Engagement in Clinical Trials Survey Report*. Medical Device Innovation Consortium. February 1, 2021. Accessed February 11, 2021. <https://mdic.org/resource/patient-engagement-in-clinical-trials-survey-report/>

SECTION 3

Report Scope and Context

Medical devices fall into multiple categories, ranging from routine items like bandages to MRI machines, diagnostics, and therapeutics, as well as highly specialized, implantable items like a heart valve or stent.

While low-risk products (Class I) are generally exempt from premarket regulatory review and most moderate-risk devices (Class II) require demonstration of substantial equivalence to a marketed product for regulatory clearance (although some 510(k)s for Class II devices require clinical data), higher-risk devices (Class III) are subject to the approval of a Premarket Approval Application (PMA). All new devices are automatically considered to be Class III if there is no predicate. A novel device may come in through the De Novo classification process if there is perception that it should not be considered Class III because general and/or special controls provide a reasonable assurance of safety and effectiveness and no legally marketed predicate exists.¹⁶ These processes require valid scientific evidence.¹⁷

This report focuses on devices that must undergo clinical testing through trials to provide safety and effectiveness data for regulatory review and decision-making. For such devices, sponsor companies (both in the United States and globally) are increasingly seeking to include patient perspectives in the design and assessment of new medical technologies. Sponsors and regulators increasingly recognize the importance of leveraging patient insights in the conduct of device clinical trials, both in selecting outcomes that matter to patients and designing trial protocols that patients will join and can complete.

To inform development of this report, MDIC undertook two important projects: (1) a broad landscape review of existing materials, literature, and resources focused on generating patient insights for clinical trials and (2) surveys of device patients and industry stakeholders to assess potential benefit for and use of patient engagement strategies for clinical trials.^{18,19}

3.1 Literature Review

The literature review reflects a broad scan of publicly available information about relevant organizations, initiatives, materials, and publications, as of December 2020. The summary provides a representative snapshot of activities and resources within the highly active and evolving field of patient engagement in clinical research.

¹⁶ *De Novo Classification Process (Evaluation of Automatic Class III Design)*. Guidance document. U.S. Food and Drug Administration. October 2017. Accessed February 11, 2021. <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/de-novo-classification-process-evaluation-automatic-class-iii-designation>

¹⁷ *Code of Federal Regulations: 21CFR§860.7(c)(2)*. FDA Regulatory Process. U.S. Food and Drug Administration. April 4, 2012. Accessed February 11, 2021. <https://www.govinfo.gov/content/pkg/CFR-2012-title21-vol8/xml/CFR-2012-title21-vol8-sec860-7.xml>

¹⁸ *Literature Review: Patient Engagement in Clinical Trials*. Medical Device Innovation Consortium. March 2021. Accessed March 19, 2021. <https://mdic.org/resource/patient-engagement-in-clinical-trials-literature-review>

¹⁹ *Patient Engagement in Clinical Trials: Patient, Industry, and Clinical Investigator Perspectives*. Medical Device Innovation Consortium. March 2021. Accessed March 11, 2021. <https://mdic.org/resource/patient-engagement-in-clinical-trials-patient-industry-and-clinical-investigator-perspectives/>



3.2 Surveys

MDIC conducted a total of three surveys between 2018 and 2019 to gather feedback from industry, patients, and investigators. For the first two surveys (which were conducted in 2018), MDIC received feedback from 53 device and diagnostic industry stakeholders²⁰ and 123 individuals identifying as patients.²¹ The goal of the complementary surveys was to inform efforts to develop guidelines for industry on how to involve patients in the design of clinical trials.²²

Key findings from the three surveys indicated a significant opportunity to expand awareness among device and diagnostic companies of the benefits and importance of patient input and leverage investigator experience with this type of work. Given the perceived barriers highlighted in the industry survey, there is a need to produce resources for device companies about how to go about gathering and employing patient input in trials. The surveys found that:

- More than half of industry respondents to the question “In your estimation, how often does your organization gain feedback directly from patients prior to finalizing a study protocol?” reported their organizations never gain patient input to protocol development, while nearly a third estimated their organizations gain input less than 25% of the time.
- Once protocols were finalized, more than 80% of industry respondents said they either never sought patient input on operational study design or did so less than 25% of the time.
- There are disconnects in the perspectives of industry respondents and patients relating to the reasons patients might decide to enroll in a clinical trial, particularly around the importance of doctor recommendations. For example, 92% of industry respondents rated a physician recommendation as “Important” or “Very Important” in a patient’s decision to participate in a clinical trial. In contrast, of patient respondents²³ who had been invited to participate in a clinical trial, 32% heard about the trial from their physician or healthcare provider. Of those who agreed to participate, only 9% of respondents marked “Doctor Recommendation” as their reason for deciding to participate in the trial. As a possible explanation for this discrepancy, 73% of the patient respondents belonged to patient organizations; they may represent a sampling of well-informed patients who do not need to rely solely on recommendations from their own healthcare providers.

²⁰ Most respondents for the industry survey were employees of medical device manufacturers (38), while only 5 identified their role as employee of an *in vitro* device manufacturer.

²¹ The patient survey was sent out to multiple patient advocacy organizations, including the American Sleep Apnea Association, American Heart Association, the DiaTribe Foundation, the Michael J. Fox Foundation for Parkinson’s Research, and Unite 2 Fight Paralysis.

²² Although these sample sizes are indicative of some patient populations and industry representatives, different patient populations have widely differing experiences, prognoses, expectations, and priorities. Likewise, the medical device industry is diverse, with different types of products requiring differing approaches to best gather insights from patients.

²³ A total of 20% of respondents were aged 45-54 years, 37% were aged 55-64, and 32% were aged 65-74. Females comprised 60%. A total of 73% belonged to patient groups, though only 38% said they were invited to participate in a trial by a patient support or advocacy group.

SECTION 4

Unique Device Trial Aspects

As medical device developers consider opportunities and approaches for engaging patients in their clinical trials, there are many lessons that can be learned from their drug and biologic development counterparts, for whom the patient engagement experience is more robust. While this field continues to evolve and mature even in the drug development arena, wherever possible, the device industry should assess best practices from across the medical product spectrum.

It is important to note, however, there are multiple aspects of medical device clinical trials that are unique, making it more challenging to replicate activities that may be suitable for drug development efforts. There are several key distinctions between device trials and drug trials²⁴ that present unique opportunities, challenges, and resource needs for engaging patient insights in the device field.²⁵ To identify and highlight those aspects for the Framework project, an MDIC Working Group evaluated a series of characteristics of device trials and prioritized them based upon their relevance for patient engagement.²⁶ The Working Group focused on four categories of device aspects: (1) Level of Invasiveness, (2) Outcomes Assessment, (3) Trial Enrollment, and (4) Trial Design. In each category, there were several important aspects identified, as well as the priority patient engagement objectives and opportunities associated with them. The following table (**Table 1**) was developed by MDIC to illustrate these topics:

²⁴ While it is also the case that surgery may sometimes be an alternative option to device use (as distinct from the cases in which surgery is central to the use of the device through implantation), for the purpose of this report and the following table, comparisons are made between devices (including those that require surgery for implantation) and drugs.

²⁵ There are times when combination approaches that involve drugs and devices are being developed, which can further complicate the design of the trial and make it both more challenging and worthwhile to engage patient input. While this paper focuses on “device-only” trials, the principles it highlights are also generally relevant for a combination therapy trial.

²⁶ Faris O, Shuren J. An FDA viewpoint on unique considerations for medical device trials. *N Engl J Med* 2017;376:1350-1357. See appendix table, reproduced from NEJM.

Table 1. Device Trial Characteristics and Their Relationship to Patient Engagement Objectives

CATEGORY	ILLUSTRATIVE PATIENT ENGAGEMENT OBJECTIVES
Elements of Level of Invasiveness: <ul style="list-style-type: none"> Implantable device External device/impact on daily life Reversibility Impact relative to disease state (early disease vs. later-stage disease) 	Understanding how device trial patient participants evaluate the benefits and risks of undergoing an invasive procedure associated with use of a device (as compared with other potential therapy options)
	Understanding how patients might evaluate various procedures related to implantation and/or use of the device, in order to (1) best explain these elements to patients and (2) consider ways to mitigate concern regarding invasiveness/mode of administration of the device (where possible)
CATEGORY	ILLUSTRATIVE PATIENT ENGAGEMENT OBJECTIVES
Elements of Outcomes Assessment: <ul style="list-style-type: none"> Selection of primary and secondary endpoints Selection of performance goals Required follow-up Reporting of side effects/symptoms by patients 	Understanding what outcomes are most relevant to the patient population and incorporate those as endpoints (where possible)
	Understanding patients' views on risk-benefit priorities
	Identifying measurement and data capture approaches that are most acceptable to device trial patient participants to maximize successful adherence to trial protocol elements
	Leveraging patient input to reduce/eliminate burdens on trial participants (including appropriate stratification of patients and effective use of mobile technology (e.g., elderly, rural populations) and other means for tracking progress on trial (e.g., measurement of symptoms, side effects, patient-reported outcomes [PROs], overall outcomes) while allowing patients to remain connected to the study and the sponsor over time
CATEGORY	ILLUSTRATIVE PATIENT ENGAGEMENT OBJECTIVES
Elements of Trial Enrollment: <ul style="list-style-type: none"> Study population (including participation by under-represented populations) Size of enrollment Patient screening/inclusion and exclusion criteria Education needs of patients (for successful participation in the trial) 	Understanding patient desires for enrolling in the trial, seeking opportunities to adjust inclusion/exclusion criteria, and making it easier to accrue patients (where possible) to enhance opportunities for broader access among the target study population
	Understanding what information is most relevant for device trial patient participants in deciding to enroll in, remain on, and be compliant participants within a trial
	Evaluating best approaches for most successfully communicating this information to patients in order to develop and convey the most relevant messaging and materials
	Determining patient interest in receiving real-time (where possible) and follow-up communication/information about their own data and the overall success/failure of the trial (data sharing/feedback loop)
CATEGORY	ILLUSTRATIVE PATIENT ENGAGEMENT OBJECTIVES
Elements of Trial Design: <ul style="list-style-type: none"> Placebo/sham procedure Crossover option Single-arm studies Unblinded studies Adaptive design Device modifications during the trial Use of real-world evidence (RWE) 	Understanding how device trial patient participants feel about a variety of trial design aspects (including use of placebo/sham, lack of control group, unmasked study arms, adaptive design, and potential to modify the device during the trial) to (1) adjust the design if possible/where necessary to facilitate success and/or (2) position patient-facing messaging/materials to speak to/address patients questions/concerns. Understanding patient perspectives on best ways to reduce/eliminate burdensome study protocol requirements including leveraging RWE and other innovations in clinical trial conduct

SECTION 5

Key Topics Overview

5.1 Invasive Procedures

A key distinction for certain categories of device trials (when compared with most drug studies) may be the requirement for patients to undergo an invasive procedure(s). There are myriad considerations for a patient in deciding whether to participate in these types of studies, including evaluating risks associated with the procedure (and postprocedure complications), trusting that the clinician is a trained specialist who can successfully conduct the procedure, and understanding the potential impact an implanted device may have on quality of life. By engaging with patients in the trial design, sponsors can develop appropriate messaging and steps in the trial enrollment process that can help to address these and other considerations for potential trial participants.

5.2 Reversibility

Unlike most drugs under study that are metabolized and cleared from the body after a defined period, devices that are implanted have a more permanent impact on the patient. Even those devices that are implanted via minimally invasive procedures may have a permanent place within the patient's body, while removal of such devices also can have significant impact (as the associated procedures are often invasive and may be life changing). An example of this can be a transcatheter coronary artery valve that must be removed via invasive open-heart bypass surgery. This lack of routine reversibility for an experimental device may be an issue of concern to patients considering enrollment in a trial. Understanding patients' perspectives on this topic can help sponsors develop messaging—including providing a level of assurance about what will happen to the patient if the study does not support marketing authorization of the device in the United States—and communication approaches to address this potential barrier to accrual. Transparency regarding this topic is important to ensure patients understand the potential permanence of a device.

5.3 Reporting Side Effects and Symptoms

In some cases, patients with devices may see their participation in the study as directly connected to the procedure and related complications. Once that period has ended, patients may be less frequently engaged with ongoing in-person monitoring than occurs in drug trials, especially when the patient does not require specific medical follow-up (e.g., ongoing infusions) to continue to "use" the device. Once a device is implanted, for example, patients may not feel the need to stay connected to the study and trial sponsor. While in the case of an implant, there typically are prospectively identified assessments postimplantation until collection of the primary endpoint data are complete; there may be missing data on side effects, symptoms, or adverse events relevant to the study. The loss of the patient to follow-up could impact the effectiveness assessment too, limiting the ability to see a true success even when it is present. Patient insights can help inform sponsors on approaches to continue to monitor the patient's progress (e.g., use of mobile digital health technology, stratification of monitoring based on special needs of certain populations, providing childcare options). This is a specific concern with investigational devices used for elective procedures, such as breast implants. While not all breast implants are implanted as elective procedures, many are, and follow-up and postmarket monitoring of the safety and effectiveness of these devices have been challenging.

5.4 Placebo/Sham Procedure

A significant issue with clinical trials relates to the need for control arms to fully evaluate the impact of the novel product. In drug trials, the prospective, double-blind,²⁷ randomized-controlled clinical trial remains the gold standard, even as innovative trial designs are gaining popularity (e.g., adaptive randomization, crossover arms). A frequent concern expressed by patients who refuse to participate in clinical studies is that they will receive placebo rather than an experimental therapy if they enroll in a trial. The use of the term “placebo” when discussing trial design with patients should be clearly defined early in the process of presenting a trial to patients to demonstrate clearly how it is operationalized in the study.

Additionally, given the variation in delivery modes for certain therapies (infusion vs. oral), it can be difficult to preserve a blinded study, making it more difficult to keep patients assigned to the control arm from dropping out. To address this concern, in some cases, sponsors have provided patients in the control arm the opportunity to “crossover” into the experimental arm if their condition progresses while on the study.

In certain device trials, where a procedure is required to implant a device, there are additional issues—practical and ethical—involved with designing a trial that will accurately measure the impact of the novel intervention. Patients who are randomized to control may either have no procedure and would thereby know they were on control or might undergo some type of “sham” procedure to maintain blinding (patients may be highly resistant to this possibility). Patient input can be very helpful as sponsors consider the best approach to addressing these topics.

²⁷ The terms “blind” or “blinded” are often interchangeably used with “masked.” When a trial is “masked” so that participants do not know if they are in the investigational arm or in the control arm, regulators will often ask sponsors to test the “mask” to ensure that it is effective.

SECTION 6

Considerations for Device Developers

In this section, we review the following key considerations for device developers seeking to pursue patient engagement:

- **Defining Objectives for Eliciting Patient Input**
- **Building Organizational Capacity**
- **Engagement Planning**
- **Tactics**

6.1 Defining Objectives for Eliciting Patient Input

There is strong impetus to encourage device developers to engage patients and patient input in their development activities, and specifically in their approach to designing and executing clinical trials/investigations. In its 2019 draft “Guidance on Patient Engagement in Medical Device Clinical Investigations,” FDA defined patient engagement as “intentional, meaningful interactions with patients that provide opportunities for mutual learning, and effective collaborations.”²⁸ FDA noted that effective engagement of patients in the development of clinical trials could result in several important outcomes, including:

- Faster study/research participant recruitment, enrollment, and study completion
- Greater study/research participant commitment, resulting in decreased loss to follow-up
- Greater study/research participant compliance resulting in fewer protocol deviations/violations
- Fewer protocol revisions
- Streamlined data collection resulting in better quality data
- More relevant data on outcomes that matter to patients

A useful definition for patient engagement in medical product development proposed in 2017 by the Drug Information Agency (DIA) states²⁹:

Meaningful engagement of patients in the development of therapeutic products refers to direct and constructive interaction with patients in various important roles, over the entire medicines life cycle (from preclinical laboratory-based studies to launch, and beyond launch for as long as that medicine is available to patients), enabling the implementation of practices and actions that are based on patient perspectives and that result in measurable outcomes that meet patient needs as well as industry needs.

²⁸ Patient Engagement in the Design and Conduct of Medical Device Clinical Investigations. Draft Guidance for Industry, Food and Drug Administration Staff, and Other Stakeholders. U.S. Food and Drug Administration. September 24, 2019. Accessed February 11, 2021. This guidance has not been finalized and as such does not represent current FDA policy. <https://www.fda.gov/media/130917/download>

²⁹ Patient Engagement. Drug Information Agency. Accessed February 11, 2021. <https://www.diaglobal.org/en/resources/areas-of-interest/patient-engagement>

In its 2016 “Guidance on Patient Preference Information,”³⁰ the FDA wrote: “Patients’ input regarding their experiences and perspectives on their disease or condition and its management may be useful throughout the total product lifecycle for certain devices, by improving understanding of the disease or condition, defining design inputs to meet needs of the patient end user, assessing outcomes most important to patients, and more.”³¹

A 2016 article in *Patient Preference and Adherence*³² outlined a useful set of activities that could involve eliciting patient input leading into, through, and after a clinical study (**Figure 1**):

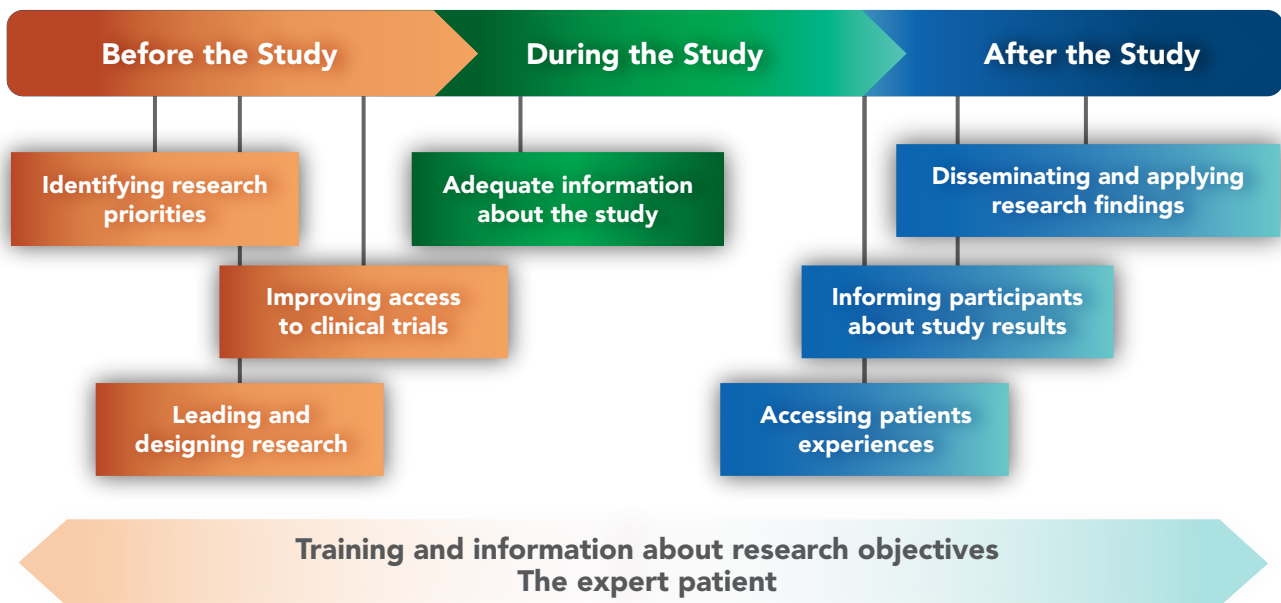


Figure 1. Activities to Involve Patient Input. Adapted from Sacristan J, et al.³²

³⁰ Patient Engagement in the Design and Conduct of Medical Device Clinical Investigations. Draft Guidance for Industry, Food and Drug Administration Staff, and Other Stakeholders. U.S. Food and Drug Administration. September 24, 2019. Accessed February 11, 2021. <https://www.fda.gov/media/130917/download>

³¹ Patient Preference Information—Voluntary Submission, Review in Premarket Approval Applications, Humanitarian Device Exemption Applications, and De Novo Requests, and Inclusion in Decision Summaries and Device Labeling. Guidance for Industry, Food and Drug Administration Staff, and Other Stakeholders. U.S. Food and Drug Administration. August 24, 2016. Accessed February 11, 2011. <https://www.fda.gov/media/92593/download>

³² Sacristan J, Aguarón A, Avendaño-Solá, et al. Patient involvement in clinical research: why, when and how. *Patient Prefer Adherence*. 2016;10:631-640. Figure used here with permission from the author.

As device trial sponsors rise to this challenge, a first critical step is to determine and clearly define the specific objectives for this effort. Why is the company interested in eliciting patient input? How will this input be used? At what time point in the development program should patient input be sought?

There are multiple answers to these questions that inform compelling reasons to proactively involve patients in the clinical development process for devices, including:

- Ensuring device meets unmet need
- Reflecting patient preferences
- Selecting device trial endpoints that matter
- Addressing barriers to trial accrual and retention
- Generating input for regulatory use
- Leveraging insights for post-approval activities

6.1.1 Ensuring Device Meets Unmet Need

The concept of “unmet medical need” (“unmet need”) is an important consideration for medical product developers and regulators. While there is no single definition of this term,³³ it is generally understood to mean a circumstance where there is a lack of effective options to treat certain conditions or groups of patients. In its 2017 report “Unmet Medical Device Needs for Patients with Rare Diseases,” the National Center for Accelerating Translational Sciences (NCATS) and FDA stated that unmet need exists when “there are no approved devices for the treatment or diagnosis of a disease or condition, or when a novel device could provide a clinically meaningful advantage over existing approved devices.”³⁴ FDA regulators have designed a variety of accelerated review processes to evaluate medical products aimed at addressing areas of significant unmet need.³⁵

Traditionally, medical professionals have been consulted by medical product developers and regulators to describe unmet need for a specific condition or among a certain patient population. More recently, sponsors and regulators have sought to engage patients directly in describing their own needs. Patients can provide detailed and nuanced feedback about ways in which their medical needs are not being met by existing treatment or device options. Engaging directly with patients to understand their condition, disease, and symptom burden, as well as the extent to which existing technologies are insufficient or could be improved, can provide important insights to guide the development path for a new device. This is often a foundational objective for patient engagement during product development.

³³ *A Multi-Stakeholder Panel Addresses the Challenges in the Lack of a Common Definition*. The Professional Society for Health Economics and Outcomes Research (ISPOR). November 6, 2017. Accessed March 4, 2021. <https://www.ispor.org/heor-resources/news/view/2017/11/06/what-is-unmet-medical-need>

³⁴ *2018 FDA/NCATS Report on Unmet Medical Device Needs for Patients With Rare Diseases*. U.S. Food and Drug Administration. August 21, 2018. Accessed February 11, 2021. <https://www.fda.gov/industry/designating-humanitarian-use-device-hud/2018-fdancats-report-unmet-medical-device-needs-patients-rare-diseases>

³⁵ *Breakthrough Devices Program. Guidance for Industry and Food and Drug Administration Staff*. U.S. Food and Drug Administration. December 2018. Accessed February 11, 2021. <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/breakthrough-devices-program>

6.1.2 Reflecting Patient Preferences

One of the most important questions regulators ask in reviewing a medical product is whether its clinical benefit outweighs its risk. Patients can provide valuable input into how they would be willing to make tradeoffs between the benefits and risks of a medical device, as well as provide insight into how they would value benefits that can impact the design and development of new technology. Patient values often differ from that of their doctors or device trial investigators, who may prioritize abnormal physiologic function over all else. Patients and their families have a deep and personal understanding of what it is like to live with a disease, and they often have valuable insights on how a device could affect their quality of life. Ultimately, it is the patients who take the risks to realize the benefits of medical therapies.

The collection and analysis of patient preference information to inform clinical development plans has emerged as an important element of the medical products landscape. Understanding how patients evaluate the benefits and risks of new medical products has become a central aspect of regulatory review for new innovations. While developing patient-preference evidence is generally a scientific (research) pursuit, patient engagement is important for the identification and inclusion of study attributes that matter most to patients.

In 2015, MDIC completed its “Framework Report on Incorporating Information on Patient Preferences Regarding Benefit and Risk into Regulatory Assessments of New Medical Technology,” providing a review of the potential use and value of this information in medical technology development and regulatory assessments and considerations for those seeking to undertake these studies and leverage their results.³⁶ In late 2016, the FDA issued a “Final Guidance on Factors to Consider Regarding Benefit-Risk in Medical Device Product Availability, Compliance and Enforcement Decisions.”³⁷

In 2016, the Biotechnology Innovation Organization (BIO) published “Key Considerations for Developing and Integrating Patient Perspectives in Drug Development: Examination of the Duchenne Case Study,”³⁸ which presented a series of practical considerations for sponsors seeking to decide if, when, and how to generate patient preference information as part of their development programs. Although this report was focused on drug development, its content may be relevant across medical products.

A 2020 “Conceptual Framework for Patient-Reported Outcome Measures for Transformative Kidney Replacement Devices” offers a detailed approach for incorporating patient perspectives into the development of medical devices, with a specific focus on including patient-reported outcome measures in clinical trials.³⁹

³⁶ *Patient-Centered Benefit-Risk (PCBR) Framework*. Medical Device Innovation Consortium. October 25, 2019. Accessed February 11, 2021. <https://mdic.org/resource/patient-centered-benefit-risk-pcbr-framework/>

³⁷ *Factors to Consider Regarding Benefit-Risk in Medical Device Product Availability, Compliance, and Enforcement Decisions Guidance for Industry*. U.S. Food and Drug Administration. December 2016. Accessed February 11, 2021. <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/factors-consider-regarding-benefit-risk-medical-device-product-availability-compliance-and>

³⁸ *Key Considerations for Developing and Integrating Patient Perspectives in Drug Development: Examination of the Duchenne Case Study*. Biotechnology Innovation Organization. June 2016. Accessed June 18, 2020. <https://archive.bio.org/key-considerations-developing-and-integrating-patient-perspectives-drug-development-examination>

³⁹ Flythe JE, Hilliard TS, Ikeler K, et al. Toward patient-centered innovation: a conceptual framework for patient-reported outcome measures for transformative kidney replacement devices. *Clin J Am Soc Nephrol*. 2020;15(10):1522-1530.

In addition to its use in understanding the benefit-risk trade-offs, patients may be willing to make, patient preference information developed with input from active patient engagement can also be used within a product label and to inform effective patient education materials. Importantly, patient preference information is increasingly being used to select clinical trial endpoints that are most relevant to patients and define effect size needed to demonstrate meaningful benefit for a device under study.^{40,41}

An oft-cited case example of this was the Enteromedics case in 2015 when the FDA used information from a study on patients' preferences while making its regulatory decision to approve a device to treat obesity.

CASE STUDY EXAMPLE:

As described by the FDA, the regulatory review and approval of the obesity device was the first time the agency had relied on quantifiable data relating to patients' views of acceptable benefits and risks associated with use of a device. These data, demonstrating how patients would make the benefit-risk trade-off, were derived from a study that estimated the maximum mortality risk patients were willing to accept for a certain amount of weight loss, and the minimum amount of weight loss sufficient to undergo the risks of a weight-loss device.

The obesity preference study allowed for systematic quantification of trade-offs patients would be willing to make among benefits, harms, and other features of weight-loss devices. While the study was designed to provide scientific data on patient preferences to inform clinical trial design for obesity devices, it ultimately resulted in data used to inform FDA's regulatory decision-making.

Sources: <https://www.rti.org/news/patient-preferences-considered-first-time-fda-decision-approve-first-kind-obesity-device>

<https://link.springer.com/article/10.1007/s00464-014-4044-2>

6.1.3 Selecting Device Trial Endpoints That Matter

Patient input during the trial design process can help sponsors better define the outcomes they are seeking to deliver with their novel products. By understanding what outcomes are most important to patients as they set up their studies, sponsors can ultimately develop data that will demonstrate impact that matters for the target population and will be meaningful during regulatory review. While informing endpoint selection is an important potential objective for patient engagement in device trials, endpoints directly impacted by the device during the trial period are most meaningful when they are clinically significant and statistically significant.

⁴⁰ Johnson FR, Zhou M. Patient preferences in regulatory benefit-risk assessments: a US perspective. *Value Health*. 2016;19(6):741-745.

⁴¹ Ho M, Saha A, McCleary KK, et al. A framework for incorporating patient preferences regarding benefits and risks into regulatory assessment of medical technologies. *Value Health*. 2016;19(6):746-750.

In addition to endpoints that are measured and reported by investigators conducting clinical investigations, the FDA has also encouraged the use of patient-reported outcomes (PROs) as primary and secondary endpoints in medical device studies as part of its commitment to increasing its use and transparency of patient input as evidence in its decision-making.⁴² This area of regulatory science and product development remains dynamic and continues to evolve. It can be useful to engage patients in assessing the relevance and ease of use of existing PRO instruments, which may not always capture the outcomes of most importance to patients.^{43,44,45}

CASE STUDY EXAMPLE:

In a study of a nipple reconstruction device in postmastectomy patients, the primary endpoint was maintenance of nipple projection length over time, likely chosen to facilitate comparison with other similar devices that have reported that metric. As a secondary measure, patient satisfaction questionnaires were also collected.

The endpoints are listed in the clinicaltrials.gov entry:

<https://www.clinicaltrials.gov/ct2/show/NCT01216319?term=nipple+reconstruction+cylinder&rank=1>

Ultimately, the study failed its projection length endpoint (maintaining 50% of its initial length over the course of 12 months). However, the patient satisfaction showed 93% were “Pleased” or “Very Pleased” with the outcome and 98% would recommend the procedure to other women.

In the publication of the study results, the authors note that (aside from safety) patient satisfaction is perhaps the most important outcome in cosmetic procedures such as this. If they had sought patient input during the design phase of the clinical trial, perhaps they would have created a combination of endpoints that factored in the outcomes of most concern to patients while addressing the risks associated with an implanted device, both of which the study would have successfully met while also representing the priorities of the patient population.

Source: Collins B, Williams JZ, Karu H, et al. Nipple reconstruction with the Biodesign Nipple Reconstruction Cylinder: a prospective clinical study. *Plast Reconstr Surg Glob Open*. 2016;4(8):e832.

⁴² *Value and Use of Patient Reported Outcomes (PROs) in Assessing Effects of Medical Devices: CDRH Strategic Priorities 2016-2017*. U.S. Food and Drug Administration. 2016. Accessed February 11, 2021. <https://www.fda.gov/media/109626/download>

⁴³ *The National Health Council Rubric to Capture the Patient Voice: A Guide to Incorporating the Patient Voice into the Health Ecosystem*. National Health Council. June 2019. Accessed February 11, 2021. <https://www.nationalhealthcouncil.org/Patient-Engagement-Rubric>

⁴⁴ Oehrlein EM, Perfetto EM, Love TR, Chung Y, Ghafoori P. Patient-reported outcome measures in the Food and Drug Administration Pilot Compendium: Meeting Today's Standards for Patient Engagement in Development? *Value Health*. 2018;21(8):967-972.

⁴⁵ Basu Roy U, King-Kallimanis BL, Kluetz PG, Selig W, Ferris A. Learning from patients: reflections on use of patient-reported outcomes in lung cancer trials. *J Thorac Oncol*. 2018;13(12):1815-1817.

6.1.4 Addressing Barriers to Device Trial Accrual and Retention

Device trials in the United States face significant challenges in enrolling the patients needed to complete evaluation of the new products. The FDA's Patient Engagement Advisory Committee (PEAC) meeting in 2017 considered data indicating that nearly half of all U.S. device trials do not meet their enrollment targets.⁴⁶ There are multiple reasons for this problem, many of which are related to the design of the study. Given the many areas of unmet need for patients with a range of medical conditions, diseases, and disabilities, as well as the financial costs to sponsors caused by delays in product development, there is urgency to improve in this area. Engaging and implementing patient feedback on the design of clinical studies can help sponsors maximize opportunities for successful trial recruitment, accrual, and retention for the duration of the trial.

There could be a variety of reasons why a patient will be interested in participating in a clinical trial, among them availability of effective standard-of-care therapy, recommendation from their physician, and understanding of how clinical trials work. Unfortunately, even once a patient has demonstrated willingness to enroll in a trial, there are significant barriers that impact ultimate entry into the trial, participation in data collection activities, and staying in the trial to completion.

Sponsors can understand and may be able to mitigate these barriers if they understand their impact on patients and are willing to consider refinements to their trial plans. It also is important to consider ways to accrue and retain patients with disabilities (such as blindness, mobility limitations, or cognitive decline) and patients from diverse demographic groups in clinical studies to ensure that results are applicable across a broad spectrum of the population.⁴⁷

Included among the most commonly cited barriers are:

- Restrictive Eligibility Criteria
- Complex Informed Consent
- Burdensome Protocols

⁴⁶ Patient Engagement Advisory Committee Executive Summary for Patient Engagement in Medical Device Clinical Trials Meeting. U.S. Food and Drug Administration. October 2017. Accessed February 11, 2021. <https://www.fda.gov/media/108162/download>

⁴⁷ Rios et al. proposed an "accessible research design" approach in their 2016 paper in the *American Journal of Public Health*, noting that "[M]aking efforts to include people with disabilities in public health, epidemiological, and outcomes studies will enhance the interpretability of findings for a significant patient population." Rios D, Magasi S, Novak C, Harniss M. Conducting accessible research: including people with disabilities in public health, epidemiological, and outcomes studies." *Am J Public Health*. 2016; 106(12):2137-2144.

6.1.4.1 Restrictive Eligibility Criteria

One often-cited reason for problems in accrual is overly restrictive inclusion/exclusion criteria in clinical studies. This topic has received much recent attention in the drug development arena, with a series of publications and recent FDA draft guidance in oncology.^{48,49,50,51} Device developers may be able to engage more patients in clinical studies by including patients in a discussion about the applicability of exclusion criteria, which, while potentially necessary to remove possible confounders to the impact of the intervention, may be unnecessarily restricting access to trials by patients who otherwise are willing to participate. Device trial sponsors can leverage patient input in evaluating routine or templated exclusions in device trials that may be outdated or irrelevant to studies of novel technology. In addition to facilitating trial recruitment, this effort can also have the benefit of producing data from the trial that are more applicable to a broader population of patients.⁵²

6.1.4.2 Complex Informed Consent Procedures

The process for meeting regulatory and ethical requirements for gaining consent from research study participants has become a cumbersome and daunting one for sponsors, investigators, and patients. While borne of noble intentions, the complexity of this component of clinical research has become a barrier to trial recruitment and has also been blamed for frequent confusion among patients about the true risks associated with study participation. Engaging patients to review informed consent materials and approaches for conducting the consent process (e.g., using plain language, translated materials, e-consent tools, and multimedia platforms) can provide sponsors with valuable insights about how best to present the specific elements and risks of their studies.⁵³

6.1.4.3 Burdensome Protocols

Similarly, trial protocols would benefit from review and feedback from patients. Increasingly, clinical study protocols rely on significant patient monitoring, which can place extensive demands on patients in terms of time, travel, physical demands, or ability to communicate about their condition. Characteristics of clinical trial participation that patients may see as burdensome include the need to travel long distances for study visits, the need for multiple study visits, and the need to undergo multiple exams or tests.

⁴⁸ Bonomi P, Blumenthal G, Ferris AS, et al. Making lung cancer clinical trials more inclusive: recommendations for expanding eligibility criteria. *J Thorac Oncol*. 2018;13(6):748-751.

⁴⁹ *Cancer Clinical Trial Eligibility Criteria: Minimum Age Considerations for Inclusion of Pediatric Patients*. U.S. Food and Drug Administration. July 2020. Accessed February 14, 2021. <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/cancer-clinical-trial-eligibility-criteria-minimum-age-pediatric-patients>

⁵⁰ *Cancer Clinical Trial Eligibility Criteria: Patients With Organ Dysfunction or Prior or Concurrent Malignancies*. U.S. Food and Drug Administration. July 2020. Accessed February 14, 2021. <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/cancer-clinical-trial-eligibility-criteria-patients-organ-dysfunction-or-prior-or-concurrent>

⁵¹ *Cancer Clinical Trial Eligibility Criteria: Brain Metastases*. U.S. Food and Drug Administration. July 2020. Accessed February 14, 2021. <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/cancer-clinical-trial-eligibility-criteria-brain-metastases>

⁵² *Patient Engagement Advisory Committee Executive Summary for Patient Engagement in Medical Device Clinical Trials Meeting*. U.S. Food and Drug Administration. October 2017. Accessed February 11, 2021. <https://www.fda.gov/media/108162/download>

⁵³ Krishnamurti T, Argo N. A patient-centered approach to informed consent: results from a survey and randomized trial. *Med Decis Making*. 2016;36(6):726-740.

Better understanding of the impact of these demands and the extent to which they create undue burden on study participants (and thereby pose a disincentive to enrollment or retention within the trial) could help sponsors identify ways to refine their protocols without compromising the integrity of the trial. Asking patients to review draft study documents, including the protocol, can highlight areas where adjustment can and should be made. This effort is often described as patient-centric trial design and can be especially impactful in studies involving patients with rare medical conditions, significant issues with mobility or stamina, or other hard-to-engage populations.^{54,55}

6.1.5 Generating Input for Regulatory Use

Regulators at the FDA have clearly stated their interest in incorporating patient input into their review process for evaluating devices, providing guidance to industry and other stakeholders and continuing to evolve Agency efforts to encourage the field to advance this work.^{56,57,58} In addition to patient preference data relating to how patients might make trade-offs between benefits of a new technology and risks, sponsors can leverage patient insights throughout their clinical development programs to develop information about their patient population's views on unmet need, burden of living with the specific medical condition, and level of satisfaction with current medical product options/standard of care. This information may be helpful to bolster regulatory submissions and other regulatory engagement.

⁵⁴ *Patient Engagement in Clinical Trial Protocol Design and Recruitment Strategies: What does it Mean for Orphan Drug Manufacturers?* Evidera. Accessed February 11, 2021. <https://www.evidera.com/patient-engagement-in-clinical-trial-protocol-design-and-recruitment-strategies-what-does-it-mean-for-orphan-drug-manufacturers/>

⁵⁵ *Are Patients at the Center of Your Trials? Using Patient Engagement and Insights to Improve Clinical Research.* Evidera. Spring 2018. Accessed February 11, 2021. <https://www.evidera.com/wp-content/uploads/2018/05/Are-Patients-at-the-Center-of-Your-Trials.pdf>

⁵⁶ *Patient Engagement in the Design and Conduct of Medical Device Clinical Investigations. Draft Guidance for Industry, Food and Drug Administration Staff, and Other Stakeholders.* U.S. Food and Drug Administration. September 24, 2019. Accessed February 11, 2021. This guidance has not been finalized and as such does not represent current FDA policy. <https://www.fda.gov/media/130917/download>

⁵⁷ "The U.S. Food and Drug Administration (FDA or the Agency) values the experience and perspectives of patients. The Agency understands that patients and care-partners who live with a disease or condition on a daily basis and utilize devices in their care may have developed their own insights into and perspectives on the benefits and risks of devices reviewed under the premarket approval, humanitarian device exemption (HDE), or de novo classification pathway. FDA believes that patients can and should bring their own experiences to bear in helping the Agency evaluate the benefit-risk profile of certain devices. This kind of input can be important to consider during FDA's decision making for these devices... FDA aims to provide a systematic way to ensure that patients are represented, and patient perspectives are considered in the decision-making process." *Patient Preference Information—Voluntary Submission, Review in Premarket Approval Applications, Humanitarian Device Exemption Applications, and De Novo Requests, and Inclusion in Decision Summaries and Device Labeling. Guidance for Industry, Food and Drug Administration Staff, and Other Stakeholders.* U.S. Food and Drug Administration. August 24, 2016. Accessed February 11, 2021. <https://www.fda.gov/media/92593/download>

⁵⁸ *Patient Preference Information—Voluntary Submission, Review in Premarket Approval Applications, Humanitarian Device Exemption Applications, and De Novo Requests, and Inclusion in Decision Summaries and Device Labeling. Guidance for Industry, Food and Drug Administration Staff, and Other Stakeholders.* U.S. Food and Drug Administration. August 24, 2016. Accessed February 11, 2021. <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/patient-preference-information-voluntary-submission-review-premarket-approval-applications>

CASE STUDY EXAMPLE:

In 2017, NxStage received clearance for an expanded indication of solo home hemodialysis use of its device based, in part, on patient preference data. The company sought this expanded indication for its device to expand treatment options for those dialysis patients who do not have care partners present and who are willing to accept the associated risks of solo treatment. It had become clear through patient engagement that some patients wanted this solo treatment option and would be willing to accept certain risks to have that opportunity.

As NxStage began to pursue the expanded indication, they intended to only conduct a qualitative survey (direct preference) to learn more about these patients' perspectives. However, feedback from FDA suggested the need to apply more statistical rigor in measuring risk and understanding patients' trade-off decisions. As a result, NxStage expanded their efforts to include a quantitative patient preference study, consulting the MDIC Patient-Centered Benefit-Risk Framework and reviewing the literature on the Obesity study (see case study example above).

In addition to informing the expanded indication, this patient preference effort also provided key insights for the company's development of a decision support tool that could supplement the product label and help with patient education.

Sources: https://mdic.org/resource/nxstage_case_study/
<https://mdic.org/wp-content/uploads/2019/04/NxStage-Case-Study.pdf>

6.1.6 Leveraging Insights for Post-Approval Activities

Once a new medical product has been approved for commercial use, sponsors continue to need to understand the views of the relevant patient population. While marketing designed to enhance awareness of the new product and promote its use can be developed using postdevelopment market research, these efforts can be informed and enhanced by leveraging patient insights gleaned during the clinical research phase. Additionally, patient input can help define opportunities for best ways to communicate the impact of the new product, while explaining its benefits and risks. Finally, patient insights can be extremely useful in activities aimed at educating payers about the value of the new product to the patient population.⁵⁹

⁵⁹ Perfetto EM, Oehrlein EM, Boutin M, Reid S, Gascho E. Value to whom? The patient voice in the value discussion. *Value Health*. 2017;20(2):286-291.

6.2 Building Organizational Capacity

Once a sponsor has clearly defined objectives for gaining patient insights, it is critical to evaluate and, where necessary, build the organization's capacity and readiness to successfully engage and implement patient input for the device development program.

Among the important elements to think about are:

- Securing internal support
- Accessing needed resources
- Conducting training
- Engaging legal and compliance

6.2.1 Securing Internal Support

Done correctly, patient engagement in medical product development is neither superficial nor episodic. Rather, the most successful efforts to leverage patient insights are those that recognize the value of this work and have embedded it into the corporate culture. Ideally, this commitment to patient engagement is held by company leaders and incentivized throughout the workforce. Securing this type of leadership support may require concentrated effort to demonstrate the importance of patient engagement activities, pointing to FDA's clear recommendation for patient input and increasing examples of return on investment in the form of streamlined clinical development programs that offer fewer study protocol amendments, enhanced accrual timelines, and improved retention rates.^{60,61,62}

It is also important to have engagement with colleagues from a variety of disciplines within the company to support a successful outreach strategy that will yield useful patient input. Increasingly, companies are staffing a patient advocacy or patient engagement function within their ranks, identifying point people to lead these efforts. Working with clinical development study teams, patient advocacy colleagues can help to identify appropriate partners within patient advocacy organizations and among the patient community. Additionally, medical affairs and commercial and policy colleagues can also play important roles in and benefit from these activities.⁶³

6.2.2 Accessing Needed Resources (expert support, funding)

Just as any prioritized activity must be appropriately resourced, successful patient engagement requires planning and appropriate budget support. Although this work is generally not costly when compared with other aspects of a medical product development program, there are costs associated with developing appropriate patient advocacy relationships, identifying and accessing expert patients/patient advisors, and hiring outside expertise (as needed) to help plan and execute events designed to bring patients together to engage their input.⁶⁴

⁶⁰ *Patient-Focused Drug Development: Collecting Comprehensive and Representative Input. Guidance for Industry.* U.S. Food and Drug Administration. June 2018. Accessed February 11, 2021. <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/patient-focused-drug-development-collecting-comprehensive-and-representative-input>

⁶¹ Levitan B, Getz K, Eisenstein EL, et al. Assessing the financial value of patient engagement: a quantitative approach from CTTI's patient groups and clinical trials project. *Ther Innov Regul Sci.* 2018;52(2):220-229.

⁶² Domecq JP, Prutsky G, Elraiyah T, et al. Patient engagement in research: a systematic review. *BMC Health Serv Res.* 2014;14:89.

⁶³ *The New Partnership Paradigm: What Patient Advocates Seek from Pharmaceutical Partners.* Syneos Health Communications. Accessed February 11, 2021. <https://syneoshealthcommunications.com/perspectives/the-new-partnership-paradigm-what-patient-advocates-seek-from-pharmaceutical-partners>

⁶⁴ *Budgeting for Engagement Activities.* Patient Centered Outcomes Research Institute. October 2020. Accessed February 11, 2021. <https://www.pcori.org/sites/default/files/PCORI-Budgeting-for-Engagement-Activities.pdf>

6.2.3 Conducting Training

Although gathering patient input into medical product development is becoming much more common, it is still a relatively new concept and many people who work in device companies may not have the needed skills to accomplish this work effectively. Working directly with patients and patient advocacy organizations requires a level of understanding and expertise that must be learned. There are myriad resources—some that can be borrowed from the drug development arena—as well as external consultants that can be used to ensure that all colleagues involved in these activities are appropriately trained.^{65,66}

6.2.4 Engaging Legal and Compliance

Conduct of clinical trials is subject to a host of legal, regulatory, and ethical guidelines. It is crucial to ensure that any patient engagement activities are compliant with these elements, as well as with additional company policies. It is advisable to begin this work by developing principles for patient engagement in clinical research for the company. Prior to finalizing any plans, communications, materials, or outreach activities, it is critical to consult legal and compliance experts within the company to ensure understanding of how engagement efforts impact upon those requirements.^{67,68}

6.2.5 Engagement Planning

In addition to ensuring that all foundational elements for an engagement program are in place, it is important to develop a detailed clinical trial patient engagement plan. There are multiple approaches for engaging patient input that have been successfully employed by product developers. While much of the experience with these activities has occurred in the drug development arena, there are opportunities for leverage in the device space.

Sponsors seeking to pursue this work often need to take the time to develop an engagement strategy designed for success. This strategy would clearly lay out the objectives of each effort; a detailed budget; realistic timelines; specific tactical steps, including identification and engagement of collaborators where appropriate (e.g., patient advocacy organizations); measurement of critical success factors; a pragmatic assessment of risks associated with this activity; and a workable plan for implementation.

⁶⁵ *Literature Review: Patient Engagement in Clinical Trials*. Medical Device Innovation Consortium. October 25, 2019. Accessed February 11, 2021. <https://mdic.org/resource/literature-review-patient-engagement/>

⁶⁶ *The PFMD Book of Good Practices*. Patient Focused Medicines Development. May 2018. Accessed February 11, 2021. <https://patientfocusedmedicine.org/bogp/book-of-good-practices.pdf>

⁶⁷ *Sponsor-Patient Interactions During Drug Development: Good Practice Insights on Patient Engagement*. National Health Council. October 2017. Accessed February 11, 2021. [http://www.nationalhealthcouncil.org/sites/default/files/Sponsor-Patient Interactions during Drug Development.pdf](http://www.nationalhealthcouncil.org/sites/default/files/Sponsor-Patient%20Interactions%20during%20Drug%20Development.pdf).

⁶⁸ *Regulations: Good Clinical Practice and Clinical Trials*. U.S. Food and Drug Administration. January 21, 2021. Accessed February 11, 2021. <https://www.fda.gov/science-research/clinical-trials-and-human-subject-protection/regulations-good-clinical-practice-and-clinical-trials>

In its 2017 Considerations Guide,⁶⁹ the Drug Information Agency (DIA) provided the following useful summary graphic to visualize these key elements of an engagement strategy (**Figure 2**):

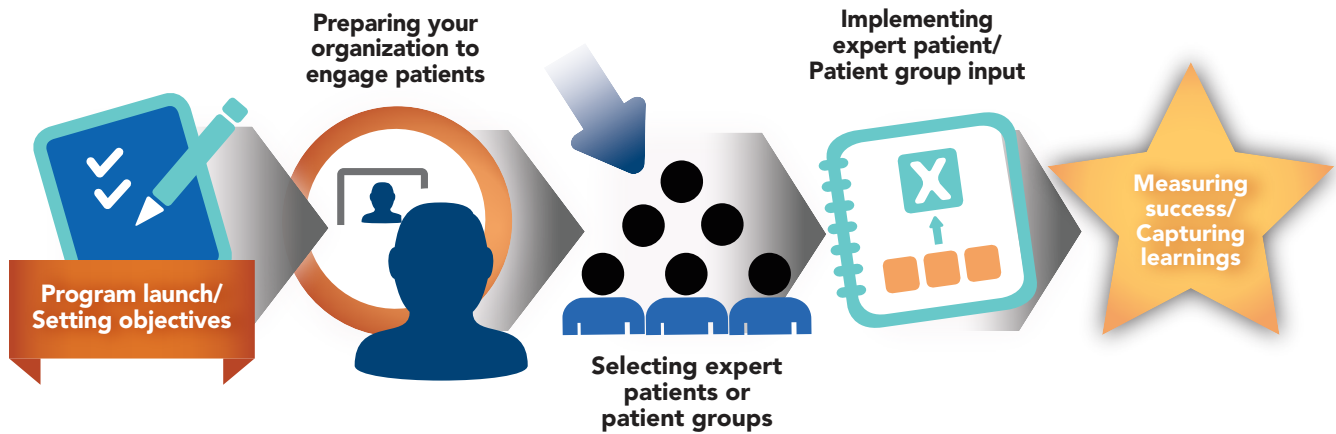


Figure 2. Key Elements of a Patient Engagement Strategy. Adapted from *Considerations Guide to Implementing Patient-Centric Initiatives in Health Care Product Development*⁶⁹

⁶⁹ *Considerations Guide to Implementing Patient-Centric Initiatives in Health Care Product Development*. Drug Information Agency. January 2017. Accessed February 14, 2021. Figure used here with permission. <https://www.diaglobal.org/~media/DIAGlobal/Files/Resources/How-We-Think/Patient-Engagement/2017/01/DIA-Considerations-Guide.pdf>

Another useful framework for planning patient engagement in clinical studies was developed in 2015 by the University of Maryland’s Center of Excellence in Regulatory Science and Innovation (M-CERSI; **Figure 3**)⁷⁰:

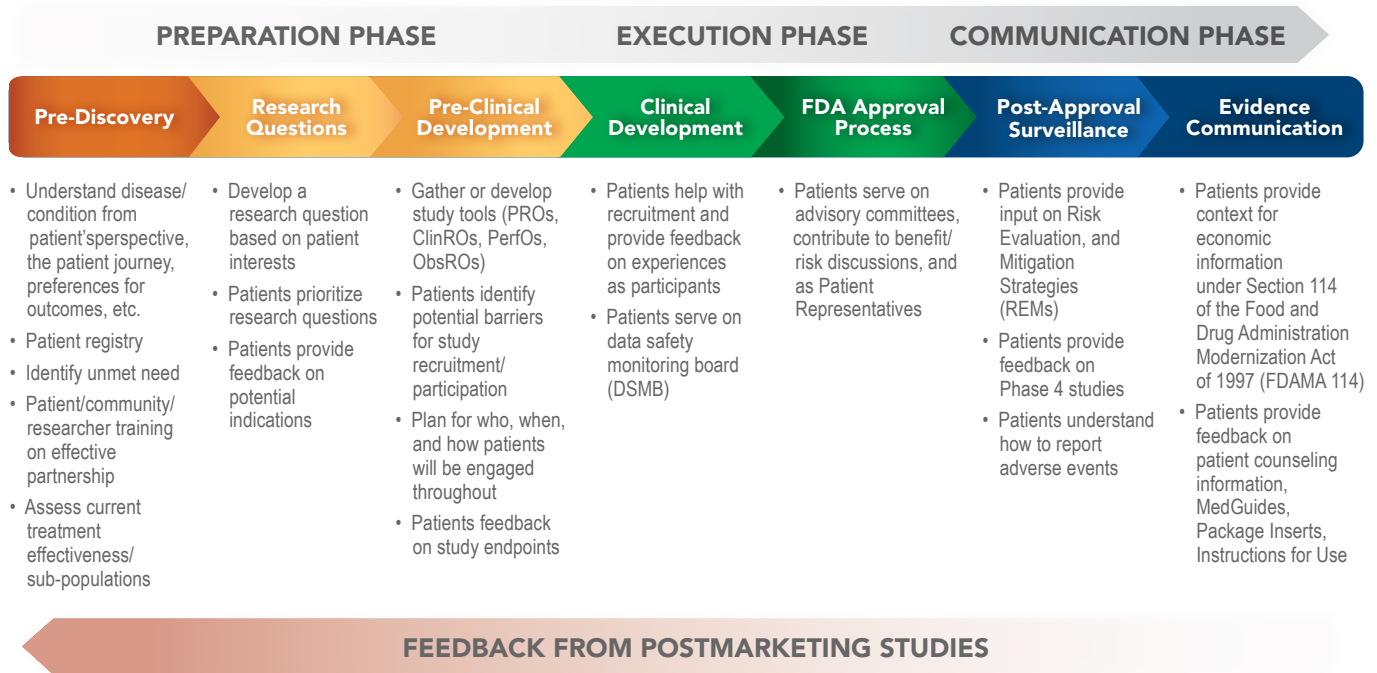


Figure 3. Framework for Planning Patient Engagements. Adapted from *Perfetto, et al.*⁷⁰

⁷⁰ Perfetto EM, Ohrlein EM, et al. *Assessing Meaningful Patient Engagement in Drug Development: A Definition, Framework, and Rubric.* M-CERSI, Baltimore, MD. 2015. Accessed February 11, 2021. Figure used here with permission from the author. <https://www.pharmacy.umd.edu/media/SOP/wwwpharmacy.umd.edu/centers/cersievents/pfdd/mcersi-pfdd-framework-rubric.pdf>

6.3 Tactics

Patient engagement in clinical research is best viewed as a continuum that occurs in different ways, for different purposes, across the lifecycle of the product development path. A good rule of thumb to guide this work is “engage early and engage often.” Although the details of each engagement plan (with whom, when, how, etc.) will be tailored to the specific development and clinical research program, there are multiple baseline tactics that should be evaluated along the way.

Among the most important tactics to consider are:

- Identifying representative patients
 - Working with advocacy organizations
 - Including patients with disabilities
- Defining patient role
- Building trust relationships
- Evaluating multiple types of activities
- Contracting and compliance
- Compensation
- Transparency/Communication
- Engaging patients in interpretation/Dissemination of findings
- Implementing patient input

6.3.1 Identifying Representative Patients

Finding the right patients to provide input to a medical product development program is critical to ensuring that the patient voice provided is relevant to the population that will access the product once it is approved.

A key stakeholder community in today’s medical product innovation landscape is the patient advocacy organization (sometimes referred to as a patient group or other similar terms). These typically nonprofit organizations have a variety of missions to serve their constituencies.⁷¹ Some are disease (or even subtype of disease) focused, while others have defined their areas of interest by different categories (e.g., therapeutic approach, prevention vs. research vs. public policy, rare diseases, pediatrics). In general, within a disease area, there may be one or several patient advocacy organizations that lead the space, and it is important for sponsors to assess the landscape in determining which groups would make the most appropriate partners based on the engagement objectives for the development program. A proposed framework for evaluating patient group expertise and assets was developed by the Clinical Trials Transformation Initiative (CTTI)⁷² and is shown as an example on the following page (**Figure 4**):

⁷¹ Terms encompassing patient advocacy organizations include disease advocacy organizations, voluntary health organizations, nonprofit research foundations, and public health organizations.

⁷² Bloom D, Beetsch J, Harker M, et al. The rules of engagement: CTTI recommendations for successful collaborations between sponsors and patient groups around clinical trials. *Ther Innov Regul Sci*. 2018;52(2):206-213.

Organizational Expertise and Assets Evaluation Tool	Pre-Discovery	Pre-Clinical	Phase 1/2/3	FDA Review & Approval	PAS*/ Outcomes
Input regarding interest of research question to patient community	•				
Providing data on unmet need & therapeutic burden	•	•	•	•	
Fundraising and direct funding for research to identify target molecules	•	•	•		
Facilitating collaboration with NIH	•				
Characterizing the disease and relevant mechanisms of action	•				
Helping define study's eligibility criteria		•	•		
Providing translational tools (assays, cell & animal models, biosamples, biomarkers, etc.)		•			
Natural history database & patient registry support	•	•	•	•	•
Input on meaningful clinical endpoints/PROs		•	•		
Assistance on regarding informed consent form		•	•		
Working with FDA regarding benefit-risk and draft guidance		•			
Accompanying sponsor to Pre-IND FDA meeting to advocate for study		•			
Fundraising and direct funding for research, trial operations support			•		
Assistance in selecting & recruiting optimum clinical sites			•		
Clinical infrastructure support			•		
Helping educate/motivate patient community & recruit for trials			•		
Providing patient feedback on participant experience			•		
Serving on Data & Safety Monitoring Board			•		
Input for any trial adaptations or modifications			•		
Accompanying sponsor to milestone meetings, e.g., after phase 2 & 3			•		
Providing public testimony at the FDA Advisory Committee & other FDA hearings				•	
Preparing submission for newborn screening when appropriate				•	
Serving on postmarket surveillance initiatives					•
Helping return study results to participants					•
Co-presenting results					•
Publications/communications regarding results					•
Feedback on how patient community views results					•
Working with payers regarding reimbursement					•

*PAS, Post-Approval Study

The highlighted cells indicate the phase(s) of the clinical trial continuum where the activity is most likely to occur.

Figure 4. Tool for Evaluating Organizational Expertise and Assets of Patient Groups.

Adapted from Bloom D, et al.⁷² (Supplemental Information)



Patient groups generally understand the needs and interests of their communities, often with significant direct connections with large numbers of patients and caregivers, and they frequently have highly sophisticated key opinion leader (clinician) networks.⁷³ Patient advocacy organization leaders can directly assist sponsors in thinking through issues relating to their clinical development program, as well as help identify, engage, and even train patients to provide input to the sponsor through the process.

It is advisable to engage with one or more patient advocacy organizations early in the device development process to build a productive working relationship and provide the foundation for collaboration in engaging patient input in the clinical trial. Selecting the most appropriate partner(s), developing a trust relationship, and putting in place the right expectations and compliance guardrails are key steps in this process. The 2015 CTTI Recommendations for Effective Engagement with Patient Groups around Clinical Trials is a useful resource for sponsors as they approach these efforts.⁷⁴

It should be noted that patient advocacy groups are not always the only or even the best source of engagement within a specific disease area, and sponsors should carefully evaluate the landscape within the community to understand any unique considerations. If possible, sponsors can also reach out to find individual “expert patients” who may not be affiliated with a specific patient organization.

There is often significant heterogeneity within patient populations, with distinctions across many domains like demographics (including minority, rural, and vulnerable populations), disabilities (such as blindness, mobility limitations, or cognitive decline), socioeconomic status, disease subtype, phase of disease/disease severity, and comorbidities. As a result, there can be many different voices within a disease/medical condition community, and it can be difficult to ensure that the insights derived from the limited number of patients engaged in a clinical development program are representative of the target population. Determining what types of voices are most relevant to a sponsor’s objectives for patient engagement is an important step to ensuring the input received is useful. Additionally, it is important to recognize that engagement across some of these domains may require extra effort to communicate and educate patients and their caregivers.

⁷³ Bloom D, Beetsch J, Harker M, et al. The rules of engagement: CTTI recommendations for successful collaborations between sponsors and patient groups around clinical trials. *Ther Innov Regul Sci*. 2018;52(2):206-213. Figure used here with permission from the author.

⁷⁴ *CTTI Recommendations: Effective Engagement with Patient Groups Around Clinical Trials*. Clinical Trials Transformation Initiative. October 2015. Accessed February 11, 2021. <https://www.ctti-clinicaltrials.org/files/pgctrecs.pdf>

A proposed rubric for considering these differing types of patient representatives was proposed by DIA in its 2017 Considerations Guide⁷⁵ and is shown here as an example (Figure 5):

TYPES OF PATIENT REPRESENTATIVES	ADVANTAGES	DISADVANTAGES
Independent patient experts	<ul style="list-style-type: none"> • Can maintain independence • Can work with multiple patient organizations • Can work in multiple areas 	<ul style="list-style-type: none"> • May have strong personal bias/blinders • May not have external validation or accountability • May not be well connected to patient community • May not be representative of the larger patient community
Patient groups	<ul style="list-style-type: none"> • Have access to varied patient communities and populations • May have significant resources and assets (e.g., patient registry, tissue banks) • Have collective knowledge of the disease • May be able to support research financially 	<ul style="list-style-type: none"> • Mission may limit ability to collaborate • Must fundraise • May have conflicts of interest with other organizations • May have limited financial resources • May not work well with related/competing organizations
Cross-disease organizations	<ul style="list-style-type: none"> • Possess cross-disease data and perspective (e.g., PatientsLikeMe, Genetic Alliance, National Health Council) 	<ul style="list-style-type: none"> • May have weaker connection to the patient community of a specific disease
Consulting organizations or other vendors	<ul style="list-style-type: none"> • Have processes in place to source and screen patients for a particular need • May be able to source for any disease 	<ul style="list-style-type: none"> • If the program objective is to develop relationships directly with patients, the consultant may be an unnecessary middle man • May not possess detailed knowledge of the disease
Lay patients (may include caregivers or those at risk for the disease)	<ul style="list-style-type: none"> • More representative of your typical patient or clinical trial participant • Less likely to be biased for or against a particular message or mission 	<ul style="list-style-type: none"> • May lack expertise in the clinical trial process or current technologies • May not be as articulate or organized in speaking to issues of interest to industry • May not understand the difference between research and standard of care

Figure 5. Rubric for Types of Patient Representatives. Adapted from *Considerations Guide to Implementing Patient-Centric Initiatives in Health Care Product Development*⁷⁵

⁷⁵ *Considerations Guide to Implementing Patient-Centric Initiatives in Health Care Product Development*. Drug Information Agency. January 2017. Accessed February 14, 2021. Figure used here with permission. <https://www.diaglobal.org/~media/DIAGlobal/Files/Resources/How-We-Think/Patient-Engagement/2017/01/DIA-Considerations-Guide.pdf>



In its 2019 draft Guidance on Patient Engagement for designing and conducting medical device clinical investigations, FDA recommended that sponsors identify patient advisors who can undertake a clearly defined role in the planning process for the study.⁷⁶

Knowing which type of patient voice is most relevant to a development program can be challenging and is certainly not an exact science. Although there is no set formula for how to approach this work, product developers seeking patient input for their clinical studies should be aware of the variations in patient experience and evaluate the extent to which the insights they receive are representative for the population under study. This concept of “representativeness” within a patient sample is well known within the clinical development arena (as clinical trials often seek statistical representativeness).⁷⁷ However, there are differing considerations—and unique challenges—associated with seeking representativeness for the purpose of engaging patient input in the design of a study, endpoints, or understanding patient priorities when it comes to evaluating benefits and risks.

In 2017, the National Health Council (NHC) issued *Tackling Representativeness: A Roadmap and Rubric*, which defined representativeness in the context of patient engagement as “a sufficient number of and types of people are included in the engagement activity to ensure that those engaged can speak on behalf of the target population. It refers to ‘who’ and ‘how many’ individuals to include in an interaction to, as closely as possible, engage with individuals that represent the broader, target patient population.” The NHC Rubric developed a roadmap for achieving representativeness (including the likely need for training for all stakeholders, and especially individual patients, to ensure that insights gained through the engagement activity reflect as broad a swath of the target patient population [including demographic diversity] as possible).⁷⁸

⁷⁶ *Patient Engagement in the Design and Conduct of Medical Device Clinical Investigations. Draft Guidance for Industry, Food and Drug Administration Staff, and Other Stakeholders.* U.S. Food and Drug Administration. September 24, 2019. Accessed February 11, 2021. This guidance has not been finalized and as such does not represent current FDA policy. <https://www.fda.gov/media/130917/download>

⁷⁷ A consensus definition of statistical representativeness within a device clinical study states: “A study measuring a sample of adequate size to ensure that the study results can be generalized to the population of interest—may be influenced by sample size, the between-subject variability, and how subjects were sampled from the population of interest.” *Patient Preference Information—Voluntary Submission, Review in Premarket Approval Applications, Humanitarian Device Exemption Applications, and De Novo Requests, and Inclusion in Decision Summaries and Device Labeling.* U.S. Food and Drug Administration. August 24, 2016. February 11, 2021. <http://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm446680.pdf>

⁷⁸ Multiple organizations, including the Patient-Centered Outcomes Research Institute (PCORI) and the National Organization for Rare Disorders (NORD) offer training for study sponsors conducting studies and for patients seeking to engage as “expert patients” or “patient advisors” in clinical research studies. *PCOR Training: A Program for Rare Disease Patient Advocates.* PCORI. November 12, 2019. Accessed March 3, 2021. <https://www.pcori.org/research-results/2015/pcor-training-program-rare-disease-patient-advocates>

Shown here (**Figure 6**) is a useful graphic representation developed by NHC to demonstrate how these concepts can work in practice⁷⁹:

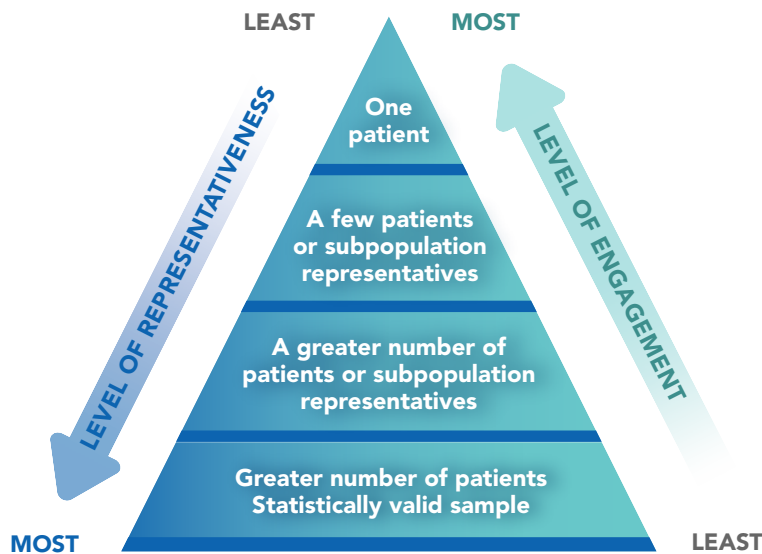


Figure 6. Representativeness Pyramid Depicting the Varying Levels of Patient Engagement Needed to Achieve Varying Levels of Representativeness. Adapted from *Tackling Representativeness: A Roadmap and Rubric*⁷⁹

6.3.2 Defining Patient Role

Successful engagement with patients (and, where appropriate, caregivers) within a clinical development program often involves developing a clear definition of what the patient’s role will be. There are multiple ways to involve patients, from providing them a proactive, governance-type of “seat at the table” with the study team, to engaging them as advisors, to offering them a more reactive role.

⁷⁹ *Tackling Representativeness: A Roadmap and Rubric*. National Health Council. November 2017. Accessed February 11, 2021. Figure used here with permission. [http://www.nationalhealthcouncil.org/sites/default/files/Representativeness in Patient Engagement.pdf](http://www.nationalhealthcouncil.org/sites/default/files/Representativeness%20in%20Patient%20Engagement.pdf).

The University of Maryland (M-CERSI) published a useful rubric⁸⁰ for thinking about the type of partnership that would be appropriate for sponsors to pursue with patients within clinical research programs (**Figure 7**):

PATIENT ROLE	EXAMPLES	ENGAGEMENT LEVEL
Partnership role	<ul style="list-style-type: none"> • Patients provide a priori and continuous consultation on outcomes of importance, study design, etc. • Patients are paid investigators or consultants • Patients have a governance role—“a seat at the table” 	High
Advisor role	<ul style="list-style-type: none"> • Patients serve as advisory committee members or provide a priori consultation on outcomes of importance and study design, but have no leadership role or governance authority 	Moderate
Reactor role	<ul style="list-style-type: none"> • Patient input is collected distally through surveys, focus groups, or interviews, but patients are not consulted directly or a priori on such things as study design and outcomes of importance • Patients are asked to react to what has been put before them rather than being the origin of the concepts of interest 	Low
Trial or study participant	<ul style="list-style-type: none"> • Patients are recruited or enrolled as study participants, but are not asked for input, consultation, or reaction 	None

Figure 7. Rubric for Patients as Partners. Adapted from *Perfetto, et al.*⁸⁰

FDA has issued draft Guidance on this topic.⁸¹

6.3.3 Building Trust Relationships

A successful patient engagement effort requires a relationship-based approach. Sponsors making the effort to build relationships with patient groups and individual patients will find that they are most effective when based on shared commitment to the effort, clear expectations, regular communications, and a common language about the project. Avoiding the perception that engagement activities are tokenism and are just being done to check a box by ensuring that all parties feel respected and able to contribute within the process is a key component of making this process meaningful.⁸²

There are multiple examples of principles for interaction that can underpin patient engagement. Device trial sponsors are encouraged to review these examples and others to develop their own set of guiding principles for approaching patient engagement within their clinical development programs.

⁸⁰ Perfetto EM, Oehrlein EM, et al. *Assessing Meaningful Patient Engagement in Drug Development: A Definition, Framework, and Rubric*. M-CERSI, Baltimore, MD. 2015. Accessed February 11, 2021. Figure used here with permission from the author. <https://www.pharmacy.umaryland.edu/media/SOP/wwwpharmacyumarylandedu/centers/cersievents/pfdd/mcersi-pfdd-framework-rubric.pdf>

⁸¹ *Patient Engagement in the Design and Conduct of Medical Device Clinical Investigations: Draft Guidance for Industry, Food and Drug Administration Staff, and Other Stakeholders*. U.S. Food and Drug Administration. September 24, 2019. Accessed February 11, 2021. This guidance has not been finalized and as such does not represent current FDA policy. <https://www.fda.gov/media/130917/download>

⁸² Domecq JP, Prutsky G, Elraiyah T, et al. Patient engagement in research: a systematic review. *BMC Health Serv Res*. 2014;14:89.

One example, implemented by pharmaceutical company UCB, relies on its “STAR” principles. The STAR approach, as published,⁸³ is shown here (Figure 8):



Figure 8. UCB Pharma’s STAR Principles for Patient Group Engagement. Adapted from Pushparajah⁸³

Another approach to guiding principles was published by the Duke Clinical Research Institute (DCRI) in 2018 (Figure 9)⁸⁴:



Figure 9. DCRI Core Principles for Patient Engagement. Adapted from Stakeholder Engagement: Guiding Principles of Patient Engagement⁸⁴

⁸³ Pushparajah DS. Making patient engagement a reality. *Patient*. 2018;11(1):1-8. Figure used here with permission from the author.

⁸⁴ Stakeholder Engagement: Guiding Principles of Participant Engagement. Duke Clinical Research Institute. Accessed February 11, 2021. Figure used here with permission. <https://dcri.org/stakeholder-engagement/>

A third set of recommendations for good versus poor practice for sponsors is provided by the NHC (Figure 10)⁸⁵:

WHAT: The Relationship	WHY: Purpose/Objective	WHEN: The Timing	WHO: The Participants	HOW: The Structure	WHERE: The Location
Establish observable, open, documented, transparent partnership(s) for the purposes of interaction. Interactions between sponsors and patients should reflect a win-win balance between partners.	Clearly define and share the specific purpose of any sponsor-patient interaction.	Interactions can and should take place prior to, in parallel with, and across all stages of a product's life cycle.	Choose appropriate participants from all partner organizations (patient community, sponsors, etc.) ideally through procedures co-created and standardized prior to the interaction.	Standardize protocols, forms, and procedures to guide sponsor-patient interactions.	The location chosen should be "neutral" so that patients do not feel unduly influenced or pressured.
Examples of Good and Poor Practices					
<p>Good Practice: The sponsor has established long-term partnerships with individual patients and patient groups that include co-development of materials and other projects.</p> <p>Poor Practice: Interactions are ad hoc and created "on the fly" without continuity.</p>	<p>Good Practice: Sponsor defines the purpose as: "Learn patient opinions on a draft clinical trial protocol to minimize trial burden on patients."</p> <p>Poor Practice: Sponsor offers the purpose only when asked, but otherwise does not make the purpose transparent.</p>	<p>Good Practice: Sponsor holds focus groups for the specific purpose of gathering patient input on how exiting therapies can be improved, which includes information on one of its approved products five years after its approval. The discussion is not focused on questions about that product, the discussion guide has been co-developed with a patient-group partner and clinical experts, and the focus groups are run by a third-party facilitator.</p> <p>Poor Practice: A sponsor makes product-specific outreach to patients at a time close to approval, but with no specific objective for the interaction.</p>	<p>Good Practice: Sponsor includes a ratio of patient-to-staff participation that ensures parity and balance.</p> <p>Poor Practice: Sponsor invites patients with early stage disease to talk about the preferences of the entire patient community (including those with late-stage disease).</p>	<p>Good Practice: Sponsor routinely uses policies and procedures co-created with patients and updates them as new information and experiences become available.</p> <p>Poor Practice: Sponsor creates policies, procedures, forms, and materials without patient input on an as-needed basis with lack of consistency.</p>	<p>Good Practice: Sponsor consistently follows co-created procedures and policies to choose a venue and mechanism to engage (e.g., in person, by phone)</p> <p>Poor Practice: Sponsor only hosts patient interactions at a company location that is not agreed upon by the patient. Sponsor does not take into account any access issues that may be specific to the patient group (e.g., wheel chair accessibility, location of restrooms)</p>

Figure 10. National Health Council's Good Practices for Sponsor-Patient Interactions. Adapted from *Sponsor-Patient Interactions During Drug Development: Good Practice Insights on Patient Engagement*⁸⁵

⁸⁵ *Sponsor-Patient Interactions During Drug Development: Good Practice Insights on Patient Engagement*. National Health Council. October 2017. Accessed February 12, 2021. Figure used here with permission. [http://www.nationalhealthcouncil.org/sites/default/files/Sponsor-Patient Interactions during Drug Development.pdf](http://www.nationalhealthcouncil.org/sites/default/files/Sponsor-Patient%20Interactions%20during%20Drug%20Development.pdf).

6.3.4 Evaluating Multiple Types of Activities

There are multiple types of patient engagement activities that can be employed to generate patient insights within a clinical development program. Depending on the objectives for engagement, sponsors may pursue individual interviews with patient group leaders or expert patients, conduct focus groups with a limited number of patients, or administer surveys to a larger cohort of patients.

Each of these transactional activities can be supported by a sophisticated use of social media platforms (e.g., posting to closed Facebook groups and discussion boards/chat rooms moderated by patient groups, leveraging Twitter using hashtags/keyword). A more passive approach that is being used increasingly has been termed “social listening,” and envisions the opportunity for sponsors to “listen in” to patient discussions to gain insights that can inform medical product development.⁸⁶

On the other end of the spectrum, patient advisory boards (PABs) made up of expert patients can be convened by sponsors for a one-time engagement or to serve in an ongoing capacity throughout the development program. In 2017, the Center for Information and Study on Clinical Research Participation (CISCRP) published “Insights and Best Practices for Planning and Implementing Patient Advisory Boards,” noting that “the practice of systematically soliciting input directly from patients on protocol designs and on other clinical research–specific support areas is still a relatively foreign concept to many sponsor organizations.” Some pharmaceutical sponsors have undertaken labor-intensive “study simulations” to gauge the extent to which planned study protocols may be acceptable to patients and to create the opportunity to modify trial designs before protocols are finalized.⁸⁸

Noting that the “development and validation of partnership models to engage patients in the design and governance of clinical research programs is still in its infancy, and approaches that can ensure meaningful and effective patient participation in research are needed,” DCRI published a review of various models for patient engagement in clinical research, citing examples of patients as advisory board members, steering committee members, or co-investigators.

6.3.5 Contracting and Compliance

Whether engaging with patient advocacy organizations or individual patients, the aspects of the engagement are best when clearly outlined and codified through appropriate contracts. It is especially important to spell out roles, responsibilities, and expectations for the sponsor and the patient/patient group representative. In its recommendations for trial sponsors, CTTI encouraged establishment of rules of engagement that would define what type of contracts would be needed, including non-disclosure agreements (NDAs) and contractual terms that address issues of privacy, kickbacks, promotion, and actual or perceived conflict of interest.⁸⁹

⁸⁶ *Social Listening to Understand the Unmet Needs of Patients*. Inspire. December 11, 2018. Accessed February 12, 2021. <https://corp.inspire.com/blog/social-listening/>

⁸⁷ *Including the Patient's Voice: CISCRP's Patient Advisory Board Panels Help Organizations Engage with Patients*. Center for Information and Study on Clinical Research Participation. November 17, 2017. Accessed February 12, 2021. <https://www.ciscrp.org/including-the-patients-voice-ciscrps-patient-advisory-board-panels-help-organizations-engage-with-patients/>

⁸⁸ *Advancing the Science of Patient Input in Medical Product R&D: An Action Collaborative*. National Academies of Science. July 2019. Accessed February 12, 2021. <https://www.nationalacademies.org/our-work/advancing-the-science-of-patient-input-in-medical-product-rd-an-action-collaborative>

⁸⁹ *CTTI Recommendations: Effective Engagement with Patient Groups Around Clinical Trials*. Clinical Trials Transformation Initiative. October 2015. Accessed February 12, 2021. <https://www.ctti-clinicaltrials.org/files/pgctrecs.pdf>

Since industry contracts are often dense and complex, thereby creating potential barriers to working with patient organizations and individual patients, the NHC is developing contract templates to support opportunities for patient engagement in clinical development activities.⁹⁰ Additional tools to advance reasonable (and more streamlined) agreements between sponsors and patient advocates (albeit with a European focus) have been created by Patient Focused Medicines Development (PFMD).⁹¹

6.3.6 Compensation (Fair Market Value)⁹²

Industry sponsors are generally comfortable engaging expert advice from clinicians throughout their development programs, with a standardized approach to contracting and compensation in consideration of the time and expertise provided. There is less experience within sponsor companies for how to work with patient advocacy organizations and individual patients in similar context. There has been uncertainty and concern about if and how best to compensate groups and individuals for providing patient insights to support clinical development activities. Sponsors need to appropriately value the expertise that patients and advocacy organization representatives are providing in this context and offer to provide a fair market value level of compensation.

To help identify best practice approaches in this category, in 2015, Patient-Centered Outcomes Research Institute (PCORI) developed the following compensation rubric based on differing levels of engagement (Figure 11)⁹³:

	ACTIVITY LEVEL	DEFINITION/SCOPE	EXAMPLE	
LEAST	I. INFORM	Simply informing	Communicating plans to the patient community	LEAST
↓	II. CONSULT	Consulting on decision	Offering opinions, advice, feedback	↓
↓	III. COLLABORATE	Deciding together Acting together	Joint decisions solicited Taking actions jointly	↓
MOST	IV. STAKEHOLDER DIRECTED	Encouraging independent initiatives	Leading to patient, caregiver, organization-generated research	MOST

Figure 11. PCORI’s Model for Addressing Fair Compensation for Engaged Research Partners Based on Engagement Activity Levels. Adapted from *Financial Compensation of Patients, Caregivers, and Patient/Caregiver Organizations Engaged in PCORI-Funded Research as Engaged Research Partners*⁹³

Additionally, NHC is producing a fair market value (FMV) calculator that can be customized by individual companies to best meet their needs.

⁹⁰ *Tools to Support Sponsor-Patient Engagement: Fair-Market-Value Calculator and Engagement Templates.* National Health Council. Accessed February 12, 2021. <https://www.nationalhealthcouncil.org/resources/fair-market-value-calculator>

⁹¹ *Guiding Principles on Reasonable Agreements Between Patient Advocates and Pharmaceutical Companies.* Patient Engagement Synapse. October 2018. Accessed February 12, 2021. <https://synapse.pfmd.org/resources/900e710d-318e-48cb-a36a-a602ba193389/guiding-principles-on-reasonable-agreements-between-patient-advocates-and-pharmaceutical-companies>

⁹² *Tools to Support Sponsor-Patient Engagement: Fair-Market-Value Calculator and Engagement Templates.* National Health Council. Accessed February 12, 2021. Figure used here with permission. <https://www.nationalhealthcouncil.org/resources/fair-market-value-calculator>

⁹³ *Financial Compensation of Patients, Caregivers, and Patient/Caregiver Organizations Engaged in PCORI-Funded Research as Engaged Research Partners.* Patient-Centered Outcomes Research Institute. June 10, 2015. Accessed February 12, 2021. Figure used here with permission of PCORI. <https://www.pcori.org/sites/default/files/PCORI-Compensation-Framework-for-Engaged-Research-Partners.pdf>

6.3.7 Transparency/Communication

Ensuring a plan for transparency, especially communication with patients throughout the development program is an important component of building and maintaining the patient engagement relationship. A seemingly mundane but important set of considerations relates to identifying the most productive format for meeting with/engaging with the patients whose insights are sought (e.g., conducting in-person meetings, phone calls, video calls, or online/email communication; selecting meeting times that work for patients' schedules).

A frequent lament by patients who have engaged with clinical trial sponsors (and participated in trials) is that they rarely see follow-up communication from the sponsor about the result of the development process. Sponsors should evaluate and build upon existing data-sharing requirements promulgated by the International Committee of Medical Journal Editors/World Health Organization (ICMJE/WHO) and develop proactive communication plans based on appropriate levels of transparency.

6.3.8 Engaging Patients in Interpretation/Dissemination of Findings

As participants in study teams or advisors to the trial, patients can have a substantial, positive role in supporting interpretation of the study findings, including driving analyses (primary and secondary) into areas where they might place more value. Additionally, engaging patients and their advocates can promote accountability throughout the study process. This aspect includes ensuring that adverse events are properly reported, fully transparent protocols are published in registries such as clinicaltrials.gov, criteria for claiming effectiveness are established, and all analyses are properly conducted and reported. In March 2019, a meta-analysis review of 126 articles stemming from PCORI-funded research projects examined the role of patient engagement in project studies, describing ways in which patients and other stakeholders contribute to various parts of the research process, including data analysis/interpretation and dissemination.⁹⁴

6.3.9 Implementing Patient Input

The process of patient engagement does not end once insights have been gathered and evaluated. Determining where patient input can impact sponsors' development strategies and clinical trial plans is crucial. For example, sponsors are encouraged to consider how they will address cases where the input received through engagement is not considered relevant or implementable. This may be the case where certain fundamental aspects of the device and related trial requirements cannot be modified. However, in those instances, patient insights can help device trial sponsors refine their patient education materials to best reflect and address patient concerns.

Additionally, it may be necessary to reconcile patient input with involvement from other stakeholders (e.g., clinicians, also FDA), especially if the feedback is not aligned or in conflict. Planning for these instances is critical, setting expectations up front, developing plans for addressing such disparities, and communicating about their reasoning and decisions in these cases.

Finally, it is crucial for sponsors to understand and leverage opportunities to incorporate patient input in regulatory submissions,⁹⁵ including the possibility of including information related to this input in product labeling (e.g., via patient-reported outcomes and patient preference information) and post-approval marketing activities.^{96,97,98}

⁹⁴ Forsythe LP, Carman KL, Szydowski V, et al. Patient engagement in research: early findings from the Patient-Centered Outcomes Research Institute. *Health Aff (Millwood)*. 2019;38(3):359-367.

⁹⁵ *Patient Preference Information—Voluntary Submission, Review in Premarket Approval Applications, Humanitarian Device Exemption Applications, and De Novo Requests, and Inclusion in Decision Summaries and Device Labeling. Guidance for Industry, Food and Drug Administration Staff, and Other Stakeholders*. U.S. Food and Drug Administration. August 24, 2016. Accessed February 12, 2021. <https://www.fda.gov/media/92593/download>

⁹⁶ Tegenge MA, Moncur MM, Sokolic R, Forshee RA, Irony T. Advancing the science of patient input throughout the regulatory decision-making process. *Learn Health Syst*. 2017;1(3):e10032.

⁹⁷ Doward LC, Gnanasakthy A, Baker MG. Patient reported outcomes: looking beyond the label claim. *Health Qual Life Outcomes*. 2010;8:89.

⁹⁸ Mercieca-Bebber R, King MT, Calvert MJ, Stockler MR, Friedlander M. The importance of patient-reported outcomes in clinical trials and strategies for future optimization. *Patient Relat Outcome Meas*. 2018;9:353-367.

SECTION 7

Opportunities for Future Work

As the field of patient engagement in clinical studies for devices evolves and expands, additional efforts could be undertaken to support sponsors, including:

- Development of device company trainings
- Development of case studies of successful activities in device trials
- Pursuit of projects to capture learnings and measure impact for the field
- Conduct of a follow-up survey of device manufacturers to compare with baseline results from the 2018 survey

It is hoped that this report provides a concise set of considerations for medical device developers to evaluate as they pursue patient engagement in their clinical trials and product development activities. Recognizing that this work is complex and made increasingly so by the heterogeneity of the device development landscape and understanding that no single compilation of information can provide everything a sponsor would need, the resources presented within this report are offered as a foundation from which sponsors can advance their efforts to generate and incorporate patient input into trial design and conduct.



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