Using Patient Preference Information in the Design of Clinical Trials Framework

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

MDIC
MEDICAL DEVICE INNOVATION CONSORTIUM

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Context and Background

Patient-centered medical device clinical trials facilitate development of innovative medical products that can make a direct and meaningful impact on the lives of patients. A patient-centered approach to clinical trial design has many important benefits, including the potential to:

- Improve patient experience in clinical trials
- Accelerate enrollment
- Improve retention and long-term follow-up
- Improve data quality
- Assure that trials are focused on outcomes that matter most to patients
- Support regulatory decision-making activities
- Assist in payer evaluations of value of new medical devices
- Help ensure new technological innovation is focused on bringing the most benefit to patients

Recognizing this potential, the U.S. Center for Devices and Radiological Health (CDRH) at the U.S. Food and Drug Administration (FDA) has introduced a variety of initiatives aimed at advancing adoption of patient engagement in device development, including establishment of its Patient Engagement Advisory Committee (PEAC) and issuance of final guidance on this topic (FDA, 2022). FDA/CDRH leadership has increasingly encouraged medical device companies to include patient perspectives throughout the medical device lifecycle to ensure that device clinical studies are evaluating what matters most to patients (FDA CDRH website).

Likewise, the Medical Device Innovation Consortium (MDIC) has been focused on efforts to provide best practices, resources, and tools for its members and the device development community. MDIC's first work product under its Science of Patient Input (SPI) initiative, the 2015 "Patient Centered Benefit-Risk (PCBR) Framework"(MDIC website), broke new ground in the advancement of techniques to characterize patient perspectives through qualitative and quantitative data collection methods for use in regulatory decision-making.

More recently, it became clear that more is needed to provide device manufacturers, clinical trial/study experts, and regulatory professionals with more examples and resources about successful ways to incorporate patient perspectives in the clinical evaluation stage of product development.

To accomplish this ongoing work, MDIC secured financial support from FDA/CDRH through a Broad Agency Announcement (BAA) grant to develop a "Framework for Patient Input in Medical Device Clinical Trials," which comprises three interrelated 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 document focuses on the first of these subprojects.

Why MDIC?

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 FDA/CDRH, industry, and key stakeholders together to share vital knowledge that can help bring safe, affordable, and effective devices to patients and providers more quickly. MDIC membership and participation are 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.

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, time, and expense of clinical research and medical device development

MDIC's SPI program (MDIC website) provides a venue for continued collaboration to advance the SPI in regulatory decision-making, including advances in methodologies, and tactical considerations for integrating the patient's perspective in the design, clinical development, and regulatory review of innovative medical technologies.

Executive Summary

Investigators, device manufacturers, regulators, payers, patient advocates, and patients share the common goal of streamlining development of better, safer medical products that can improve outcomes for an array of serious diseases and conditions. A rigorous clinical trial is often a key requirement for developing the evidence needed to ensure that a new device can be safe and effective.

Some stakeholders suggest that patient preferences within a disease community may not align with traditional clinical outcome measures and can vary widely based on a variety of factors. Most stakeholders in the medical device ecosystem agree, however, that patient preference and clinical outcome measures should not be viewed as "either/or" but rather as an area where important work needs to be done to align and integrate the two using reliable methods and sufficient basis for generalizability to the population under consideration. For this reason, development of robust quantitative tools offers the opportunity for sponsors and regulators to seek ways to better evaluate what matters most to patients in the product development and regulatory review processes.

This framework is focused on providing device clinical trial[1] sponsors and the broader medical device community an actionable set of learnings and compendium of best practice information on approaches for integrating patient preference information (PPI) into clinical trial design.

These learnings are derived from engaging experts and review of five recent initiatives that have been distilled into case examples (one in Parkinson's disease, two in heart failure, one in mitral valve disease, and one in obesity).

[1] Throughout this framework, the term "clinical trial" will be used to discuss the full scope of prospective studies conducted by device sponsors in their development programs (including those leading up to regulatory submission and those conducted in the postmarketing setting or for label expansions).

With this framework, Medical Device Innovation Consortium's (MDIC's) goal is to support efforts by medical device sponsors to utilize PPI during the design of their clinical trials. This framework proposes a series of steps for device sponsors to take when seeking to leverage PPI for clinical trial design (**Figure 1**).

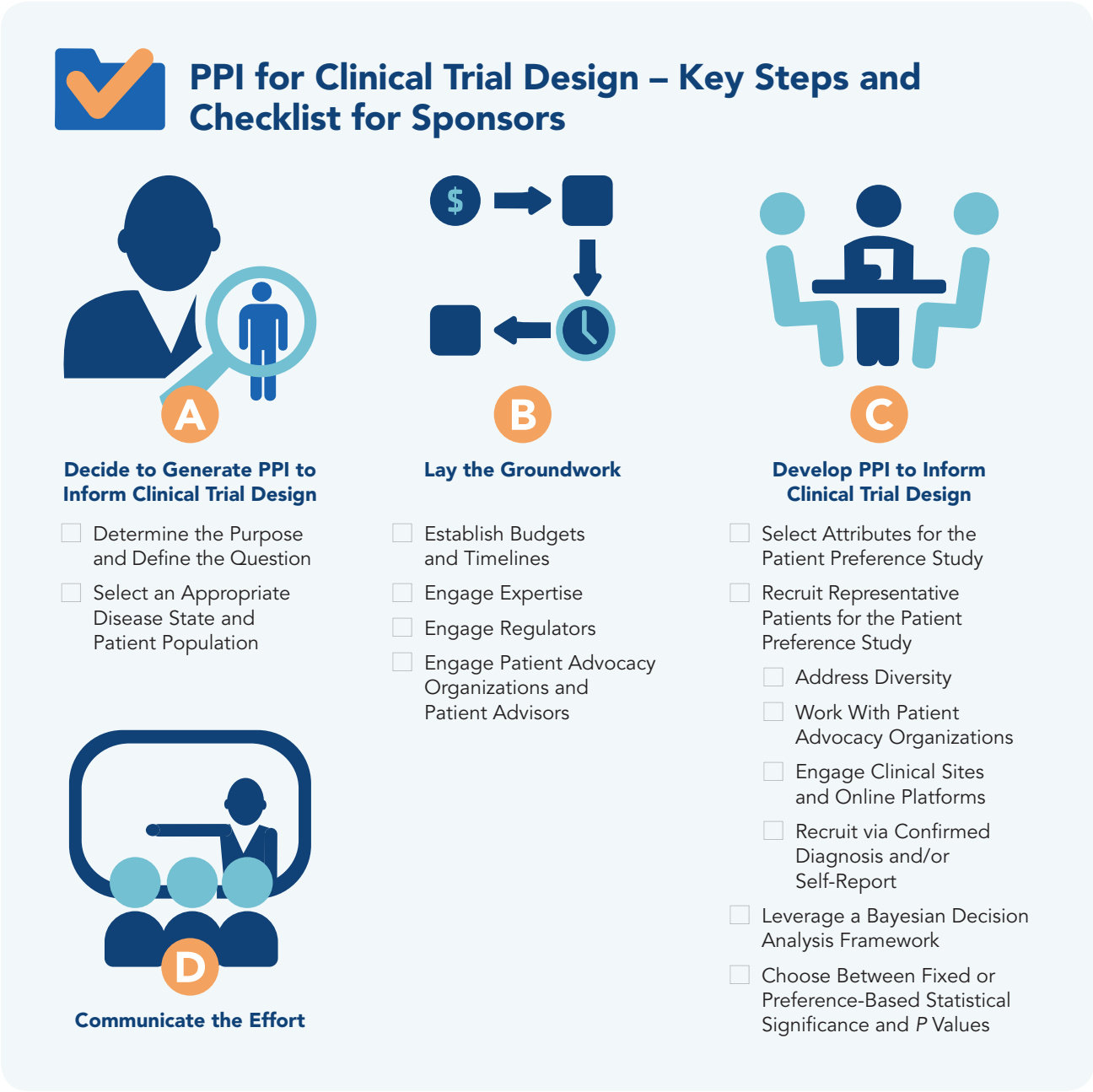


Figure 1. Key steps and checklist for sponsors considering incorporating patient preference information into clinical trial design.

While PPI can be useful to sponsors at any stage of product development, there are several broad categories of opportunity to consider, including the predevelopment stage, the early development stage, and the later stage in the development process. PPI can be used to inform decisions about design of a composite endpoint and to address statistical considerations. PPI developed with the input of diverse populations can be useful in helping to maximize opportunities of recruitment and retention of underrepresented populations in trials.

To ensure that PPI is reflective of the intended population for a potential medical device, it is important to be as confident as possible that the participants in the patient preference study accurately reflect the population with the disease or condition under study.

A critical component of the process for developing PPI to inform clinical trial design is ensuring adequate recruitment (numbers and representativeness) within the patient preference study sample. A large enough sample size in the patient preference study may be needed to help understand preference heterogeneity within a disease population. This would allow for subgroup analyses that can elucidate distinctions in priorities and risk tolerances among different types of patients.

This framework provides detailed information for sponsors to consider in engaging the appropriate expertise and stakeholders (especially patient advocacy organizations) as they plan and execute patient preference studies to inform clinical trial design. A key consideration for clinical development teams within sponsor organizations is understanding the trade-off between costs and benefits for developing and implementing PPI within their clinical trial design efforts.

An important lesson from the case examples presented in this framework is the need to proactively engage with regulatory officials from the beginning of any effort to develop PPI in support of medical device clinical trial design. For example, sponsors should be aware of regulatory considerations and engage regulators in their decision-making about attribute selection for a patient preference study to ensure a clear, agreed-upon "crosswalk" from the patient preference study attributes to the endpoints in the clinical trial. Additionally, sponsors will need to engage with regulators in discussions about any effort to leverage PPI for use in the statistical evaluation of trial data.

One potential approach discussed in this framework to incorporate PPI in the development of patient-centered significance level thresholds is use of a Bayesian decision analysis (BDA) framework. The BDA framework provides a systematic, quantitative, and transparent approach to setting the statistical significance threshold for a clinical trial. In this way, the overall consequences of approving an ineffective and possibly harmful treatment are balanced against the consequences of rejecting an effective treatment using insights gathered from the patient population under study.

In addition to incorporating PPI related to risk tolerance among patients, the BDA framework can also evaluate trade-offs relating to time preferences among patients (e.g., how long would patients be willing to wait for a novel device). Patients with a serious condition, rapid progression, and lack of effective therapy or standard of care may be willing to accept more uncertainty about the likely benefit and probable risk of a new device in exchange for accessing it sooner. It may be possible to design a clinical trial that incorporates higher levels of uncertainty and run it with fewer patients over a shorter time frame.

This framework provides a body of information and case examples to help move the device field forward toward more patient-centered clinical trials. As the body of evidence supporting the feasibility of these approaches grows, MDIC envisions that all stakeholders will develop additional confidence and comfort with using PPI to design the most streamlined and efficient clinical trials possible in the development of medical devices, yielding outcomes that systematically include the benefit-risk preferences of patients.

Sections 1-6:
Using Patient Preference Information in the Design of Clinical Trials Framework

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

SECTION 1

Introduction: Integrating Patient Preferences Into Device Clinical Trial Design

This framework is focused on providing device clinical trial[2] sponsors and the broader medical device community an actionable set of learnings and compendium of best practice information on approaches for integrating patient preference information (PPI) into clinical trial design. These learnings are derived from engaging experts and review of several recent initiatives that have been distilled into case examples. With this framework, the Medical Device Innovation Consortium's (MDIC's) goal is to support efforts by medical device sponsors to utilize PPI during the design of their clinical trials.

Main topics addressed in this framework include:

- **Opportunities** for using PPI to inform clinical trial design
- **Key steps** in developing PPI for the purpose of informing clinical trial design, including **engaging relevant stakeholders** and considerations for **selecting attributes** for the patient preference study
- **Approaches for applying** PPI in the design of clinical trials, including **endpoint selection and evaluation**
- Describing how use of PPI in one specific model—Bayesian decision analysis (BDA)—may **facilitate the statistical design aspects** of a clinical study
- **Implications** for future device trials and areas where **more work** is needed

[2] Throughout this framework, the term "clinical trial" will be used to discuss the full scope of studies conducted by device sponsors in their development programs (including those leading up to regulatory submission and those conducted in the postmarketing setting or for label expansions).

SECTION 2

Opportunities for Using Patient Preference Information to Inform Device Clinical Trial Design

2.1 What Is Patient Preference Information (PPI)?

As defined by the U.S. Food and Drug Administration's (FDA's) Center for Devices and Radiological Health (CDRH), PPI is the assessment of "the relative desirability or acceptability to patients of specified alternatives or choices among outcomes, timing of the outcomes, or other attributes that differ among alternative health interventions." (FDA, 2016). Patient preference studies generate data on patients' preferences, priorities, and values for commercially available or investigational health-related products. A frequent goal for gathering this information is to ensure that medical products are developed by sponsors and assessed by regulators with the experience, needs, priorities, and insights of patients in mind.

PPI is often developed through survey techniques designed to elicit preferences from a targeted patient population about how these patients in this population would make informed decisions based on benefits and risks of a medical technology. In most cases, patients with a specific medical condition are queried through sophisticated survey methods aimed at addressing a unique research question about outomes or attributes related to therapy alternatives and asked to make choices or trade-offs that reflect their preferences. These choices may include decisions relating to the magnitude of the potential treatment effects and severity of potential risks, including death.

An important and relevant objective of PPI studies is to quantify the weights and/or threshold values for trade-offs among each potential outcome or attribute of a device, representing patients' prioritization of the outcomes or attributes. These data can be used in multiple ways, including informing prioritization of clinical outcomes, setting performance goals, supporting the benefit-risk decision-making process, and evaluating innovative medical device technology from the perspective of what is important to patients.

PPI is different from patient-reported outcomes (PROs) and patient engagement (**Figure 2**). PROs are outcomes that can be collected as part of a clinical trial and measure how patients feel and function (FDA, 2022).[3] While PROs are not addressed directly in this framework, PPI may influence the choice of PROs selected as primary or secondary endpoints in clinical trials, and PROs could inform attributes for a patient preference study. Likewise, developing PPI is not the same as patient engagement and does not directly foster study participation and retention, concepts that are also not directly addressed in this framework.

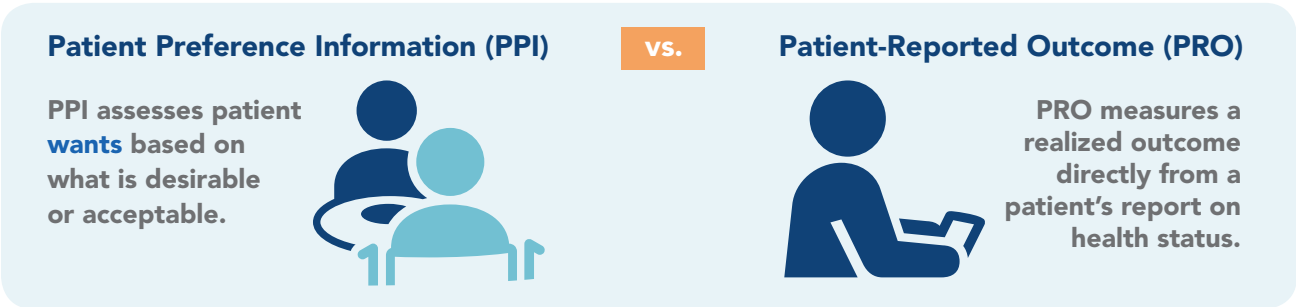


Figure 2. Differences between patient preference information and patient-reported outcomes. Adapted from *Hauber B, Virtual ISPOR-FDA Summit 2020. September 29, 2020.*

[3] There are important differences between patient preference information (PPI) and patient-reported outcomes (PROs). A 2019 National Health Council webinar provides an overview of these distinctions. Accessed March 4, 2021. https://nationalhealthcouncil.org/coa-series-measuring-patient-experiences-distinguishing-between-patient-reported-outcomes-and-patient-preferences/

2.2 Recent History of PPI and Medical Devices

Efforts to incorporate PPI into the development and regulatory review of medical products (including medical devices) have been underway for some time, as sponsors and regulators sought better ways to measure and evaluate how patients make benefit-risk trade-off decisions. Key milestones in this history include CDRH guidance documents (beginning with a benefit-risk guidance issued in 2012 and most recently in 2019) (FDA, 2019), a CDRH-sponsored patient preference study relating to obesity and weight-loss devices (FDA CDRH website), and publication of MDIC's "Patient Centered Benefit-Risk (PCBR) Framework" (2015, MDIC website). The timeline (**Figure 3**) provides a history of key FDA guidance documents:

Figure 3. Timeline of FDA guidances related to measuring and evaluating how patients make benefit-risk trade-off decisions.

More recently, the FDA reviewed PPI submitted in select regulatory submissions for label expansion for medical devices (Benz, 2020) and has issued guidance about the submission of PPI in support of marketing applications (FDA website). Through October 2020, 23 PPI studies have been undertaken or completed by sponsors for a variety of medical device applications (FDA CDRH website).

2.3 Focus of This Framework: Use of PPI in Design of Device Clinical Trials

This framework leverages the foundation laid in 2015 with MDIC's "PCBR Framework" (MDIC website), which provides detailed information about designing a patient preference study in support of medical device programs, including considerations for which type of situations might be most amenable to developing and utilizing PPI. The factors considered in terms of amenability include types of disease or condition, heterogeneity of patient population, differences in preference decisions among patients and providers, when clinical experience with a disease or device might be highly subjective, or within rare diseases. Sponsors and stakeholders involved in device development are encouraged to reference the MDIC "PCBR Framework" if they decide to conduct a PPI study to inform the design of a clinical trial.

The remainder of this framework provides information for sponsors and other stakeholders considering developing PPI for the *specific purpose of informing the design of medical device clinical trials.*

SECTION 3

Presenting Lessons Learned From Case Examples[4]

Recognizing the need to consider lessons learned from case examples and develop evidence to help sponsors evaluate opportunities for pursuing the approach described in this framework, MDIC launched two member-driven projects. One was focused on Parkinson's disease (MDIC-PD) and the other focused on heart failure (MDIC-HF). These efforts were overseen by member-driven working groups comprising a cross section of stakeholders (including industry, patients, and regulators) (MDIC website). Additional case examples gathered by MDIC members and participants of the working group (detailed in the appendix of this framework) provide opportunities for additional learnings and evidence to support the use of PPI in clinical trial design:

1. **Patient Preference Study Design Process (MDIC-PD):** This initiative involved a patient-centered outcomes research (PCOR) project focused on Parkinson's disease (PD) and a subsequent Bayesian design analysis (BDA) modeling of that data.

   The goals of the MDIC-PD project were to identify endpoints relevant to patients and appropriate for FDA review, elicit risk tolerance, and design a BDA model.[5] The approach involved gathering PPI from patients with PD through a study (MDIC website) conducted by RTI Health Solutions and analyzing the data using a BDA model developed by Massachusetts Institute of Technology (MIT) researchers.[6] Assessment of the PD project included a public workshop and two manuscripts, (Hauber, 2021 and Benz, 2021).

2. **A Multi-Stakeholder Collaboration Approach to Patient Preference Studies (MDIC-HF):** The second project involved six device-manufacturing companies focusing on heart failure (HF), with the goal of developing PPI related to HF and acceptability of device use for people with this condition, rather than for a specific device development program.

   The PPI study was conducted by the Duke Clinical Research Institute (DCRI)[7] with the goal to inform future HF device clinical trials. Subsequently, the data have been incorporated into a BDA model by Quantitative Life Sciences (QLS).[8]

[4] Detailed summaries of the case examples referenced in this framework can be found in the appendices.

[5] A Bayesian decision analysis (BDA) approach balances type I and II errors and, in certain cases such as diseases with unmet medical needs, could potentially support studies with smaller patient sample sizes and tolerable type I error rates higher than 5%. Type I and II errors are assigned different costs, considering balance between the costs associated with the use of an inferior treatment during and after the clinical trial. Given these costs, other population parameters, and prior probabilities, it is possible to compute an expected cost for any fixed-sample clinical trial and minimize the expected cost over all fixed-sample tests to yield the BDA-optimal fixed-sample trial design.

[6] MIT Management Sloan School. Accessed March 3, 2021. https://mitsloan.mit.edu/faculty/directory/andrew-w-lo

[7] Duke Clinical Research Institute. Accessed March 4, 2021. https://dcri.org/shelby-d-reed-phd/

[8] Qualitative Life Sciences. Accessed October 6, 2021. https://www.qlsadvisors.com

3. **Selecting Endpoints for Clinical Trials (Abbott-Heart Failure):** One MDIC member company (Abbott) contributed lessons learned from their independent preference study for patients with HF that provided additional insights for the MDIC-HF project described above and has provided input for the selection of endpoints for future HF clinical trials.

4. **Establishing Clinically Relevant Trial/Study Thresholds for Success Using PPI Data (Edwards-Heart Valve):** One MDIC member company (Edwards)[9] contributed the results of its use of PPI and planned use of the QLS BDA model to identify the optimal non-inferiority margin and inform significance from a patient perspective for an ongoing clinical trial.

5. **A PPI-Based Model for Determining Endpoint Thresholds (CDRH-Obesity):** CDRH conducted a proof-of-principle study on the preferences of participants with obesity regarding the use of medical devices to achieve weight loss (FDA website) and retrospectively analyzed these results through a BDA model (Chaudhuri et al., 2018; Soekhai et al., 2019). Information from the study was considered in the January 2015 regulatory approval by the FDA of the EnteroMedics Maestro Rechargeable System for weight loss. In addition, this effort led to development of a "calculator" tool to evaluate other weight-loss devices (Ho et al., 2015).

Taken together, these case examples summarize the lessons learned in this document.

[9] Edwards Life Sciences Corp. Accessed March 4, 2021. https://www.edwards.com/

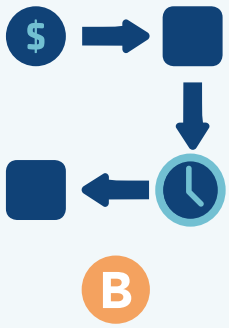
SECTION 4

Developing Patient Preference Information to Inform Device Clinical Trial Design

PPI for Clinical Trial Design – Key Steps and Checklist for Sponsors

Decide to Generate PPI to Inform Clinical Trial Design

- ☐ Determine the Purpose and Define the Question
- ☐ Select an Appropriate Disease State and Patient Population



Lay the Groundwork

- ☐ Establish Budgets and Timelines
- ☐ Engage Expertise
- ☐ Engage Regulators
- ☐ Engage Patient Advocacy Organizations and Patient Advisors

Develop PPI to Inform Clinical Trial Design

- ☐ Select Attributes for the Patient Preference Study
- ☐ Recruit Representative Patients for the Patient Preference Study
  - ☐ Address Diversity
  - ☐ Work With Patient Advocacy Organizations
  - ☐ Engage Clinical Sites and Online Platforms
  - ☐ Recruit via Confirmed Diagnosis and/or Self-Report
- ☐ Leverage a Bayesian Decision Analysis Framework
- ☐ Choose Between Fixed or Preference-Based Statistical Significance and *P* Values

Communicate the Effort

Figure 4. Key steps and checklist for sponsors considering incorporating patient preference information into clinical trial design.

4.1 Deciding to Generate PPI to Inform Clinical Trial Design

4.1.1 Determining the Purpose and Defining the Question[10]

PPI USE IN CLINICAL TRIAL DESIGN

1. Define primary and secondary endpoints
2. Design composite endpoints
3. Determine endpoint weighting
4. Evaluate statistical components
5. Identify subpopulations

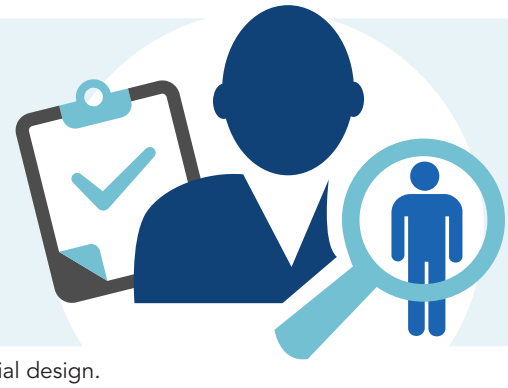


Figure 5. Uses for patient preference information in clinical trial design.

In seeking to discover, prioritize, and quantify patient preferences, sponsors should determine the purpose for collecting PPI, which will then dictate the appropriate timing for this work in relationship to design and execution of the clinical trial (**Figure 4**). While PPI can be useful to sponsors at any stage of product development (Soekhai et al., 2019), there are several broad categories of opportunity to consider (**Figure 5**):

- In the *predevelopment stage*, sponsors may find PPI helpful to identify and prioritize gaps in the treatment landscape and unmet needs for a particular disease or condition, as well as inform criteria for making go/no-go decisions. Understanding the preferences of patients on these topics can help sponsors refine the development of the device itself, as well as the approach to planning a clinical study.

- In the *early development stage* (generally when planning/executing the early feasibility study or EFS[11]), sponsors may find it valuable to generate PPI to inform the design of the pivotal clinical study, including the consideration of primary and secondary endpoints (including performance targets) that may more directly reflect outcomes considered most important to patients.

- When available, robust PPI could be used to inform decisions about design of a composite endpoint within a clinical trial and how to appropriately weight each element within the composite.[12] Complexity can occur when there is misalignment between composite endpoints[13] traditionally used in clinical trials and individual attributes of a device that emerge as being of most importance to patients. For example, a standard composite endpoint is often used, but the PPI may demonstrate that one of the components is more important. This information could be used in discussions with clinicians, regulators, and other stakeholders to focus on one or more component of a composite endpoint rather than the composite itself.

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[10] Discussion of how PPI can inform discussions with and decisions by payers is outside the scope of this project and the subject of a separate value assessment project led by MDIC.

[11] An early feasibility study (EFS) is a limited clinical investigation of a device early in development. It typically enrolls a small number of participants, is used to evaluate the device design concept with respect to initial clinical safety and device functionality, and may guide device modifications. An EFS is also known as a pilot study.

[12] Many therapeutic device areas will not have robust PPI available at the outset of their development programs.

[13] "A composite endpoint consists of at least two or more distinct endpoints, called component endpoints. Because of the need to observe a certain number of primary endpoints to achieve adequate statistical power for a study, investigators opt to use component endpoints that contribute to an overall composite event rate." McCoy CE. Understanding the use of composite endpoints in clinical trials. *West J Emerg Med.* 2018;19(4):631-634. Accessed March 4, 2021. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6040910/

- It is common in device clinical trials for the sponsor to include the components of a composite as secondary endpoints. For example, survival is generally included in a composite endpoint, and may also be a secondary endpoint of considerable interest to the sponsor. The methodology discussed below may allow for alternative analyses of these secondary endpoints; using patient preferences regarding the relative importance of the secondary endpoints could be informative.

- Sponsors may be able to leverage PPI to address statistical considerations for the clinical trial (e.g., sample size, type I error rates) that may allow for execution of a more targeted clinical study, focused on outcomes and levels of certainty that could result in much more efficient trials, depending on which outcomes patients prioritize.

- At this point in the development process, patient preference studies may also help sponsors identify clinically relevant subgroups in which certain treatment benefits are considered more valuable and could therefore help the sponsor focus the trial on the most relevant indications for use.

PPI developed with the input of diverse populations within a disease state or condition may also be useful to help sponsors design trial protocols that reflect the preferences of those groups of patients. This could help sponsors maximize opportunities for recruiting, enrolling, and retaining underrepresented populations in clinical trials.

- *Later in the development process*, device sponsors may be in the process of designing a clinical trial, or an investigational device exemption (IDE) that has already been approved by FDA/CDRH. In these cases, it is essential that the attributes chosen for prioritization and quantification in a related patient preference study align as closely as possible with the outcomes or endpoints already chosen by the investigators for the pivotal trial.

- And, while not the specific topic of this framework, PPI is also used to inform benefit-risk decision-making.

The earlier a patient preference study is conducted, and the more buy-in from clinical and regulatory stakeholders[14] a sponsor has in the process, the more likely it is to generate robust scientific evidence that could impact the regulatory decision.

4.1.2 Selecting an Appropriate Disease State and Patient Population

If the PPI is intended to apply to the regulatory context, it is important that the disease state and targeted patient population for the patient preference study are as closely aligned with the product's targeted indication as possible (e.g., disease progression and severity). Device indications generally follow the inclusion/exclusion criteria of clinical trials used for regulatory authorization. Therefore, the PPI will need to involve patients with the characteristics of the clinical trial population. The purpose of PPI is to provide sponsors and regulatory reviewers with a detailed snapshot of the perspective of the patient population the product is designed to treat. Patient preference studies have demonstrated that the preferences of individuals with the same diagnosis can vary depending on their disease state and personal perspectives (van Overbeeke et al., 2019). While it is helpful to align the disease state and targeted patient population for the patient preference study as closely with the product's targeted indication as possible, it may also be possible to recruit a broader group for the patient preference study and then conduct a subset analysis on patients that more closely align with the specific indication.

[14] Engaging the Centers for Medicare & Medicaid Services (CMS) in the PPI study design and results is also potentially important. Many sponsors are engaging CMS for protocol review to gain approval prior to starting the clinical study. However, these topics are not the subject of this framework.

However, there are some situations where it might be appropriate for a sponsor to gather PPI in a general disease state for the purpose of understanding an overall patient population's perspective in their evaluation of alternative treatment options. The MDIC-PD, MDIC-HF, and CDRH-Obesity studies were examples where the patient preference studies were not targeting a specific treatment, but instead were aimed at patient preferences more generally while understanding the existing treatment landscape and the new product development outlook. For example, in the MDIC-PD case example, the applicability of the findings from the patient preference study may be most immediate in helping to inform product development for new neurostimulation devices since there are currently few new technologies in the pipeline for this population.

It is also important to consider the potential for significant heterogeneity within patient populations that exists for various medical conditions. Patient preferences may vary based on the diversity of observable demographic characteristics (e.g., gender, age), environmental factors (e.g., culture, community), experience (e.g., disease and/or treatment history), and psychological traits (e.g., risk tolerance, comfort with new technology). These factors can impact the ability to successfully apply PPI to study design. This may be especially important to assess in disease states where some subgroups of patients might be much more willing to accept higher levels of risk than others with the same condition. When considering the integration of PPI in a regulatory context, it is a good idea for sponsors to include discussion of the planned PPI patient cohort with FDA through the pre-submission process.

4.2 Laying the Groundwork

4.2.1 Establishing Budget and Timelines

Once the purpose for developing PPI is defined and an evaluation of the appropriateness of the patient population has been made, it is important that sponsors seeking to pursue this approach begin with a realistic understanding of the logistics, costs, and timelines involved in the process. Planning, launching, and completing a patient preference study and analysis can take a year or more and require significant resources. Depending on the size of the study, recruitment methods, and level of qualitative work needed to develop the attributes, a study can range into the hundreds of thousands of dollars.

It may be possible to mitigate costs and time requirements by dividing the patient preference study into multiple phases, beginning with one in which attributes of the disease and the treatment that are important to patients are identified and one in which the extent that these attributes matter to patients is assessed.

If a patient preference study is initiated after endpoints have been determined in the clinical trial design, then a separate effort to identify attributes may be unnecessary. In this case, the patient preference study can be initiated, completed, and analyzed while the sponsor is in the pre-submission discussions of the IDE, something which has been discussed by FDA in recent guidance.[15]

In either case, while the extent of effort required to select the attributes will vary depending on how much is already known about a particular condition, it is recommended that sponsors consider conducting patient preference studies early (ideally beginning a year before IDE submission or, if need be, in parallel to design verification and validation processes) to develop and prioritize the attributes of the device and the disease that the device is intended to treat that are most important to the patient population that will be studied in the eventual clinical trial.

[15] The Investigational Device Exemption benefit-risk guidance (2017) includes a statement on page 16 about "consideration of patient preference information." Accessed September 7, 2021. https://www.fda.gov/media/92427/download

Other ways that a sponsor could limit potential costs of a patient preference study include:

- Leveraging existing studies, including the opportunity for PPI studies to help inform standards and other technical or policy efforts
- Where possible, recruiting a broader group of participants and conducting subgroup analyses
- Limiting patient preference study attributes by having a very narrow/focused research question
- Developing collaborations with other sponsors (e.g., transcatheter aortic valve replacement [TAVR], cardiac stents, or knee arthroplasty implants) so that sponsors can share the costs and results of the PPI study to benefit all manufacturers who are active in the disease or device area
- Activating more sites for a PPI study, which could shorten timelines and enhance generalizability assumptions, while ensuring that quality and added cost considerations are not undermined

4.2.2 Engaging Expertise

Conducting a robust patient preference study requires appropriate rigor and technical expertise to generate data acceptable for use in clinical trial design. Sponsors should consider engaging recognized experts in conducting patient preference studies and experts who also have demonstrated ability to recruit the appropriate type and number of patient preference study participants (as was done in both the MDIC-PD and MDIC-HF studies, with RTI Health Solutions [RTI] and Duke Clinical Research Institute [DCRI], respectively). MDIC maintains a list of consulting firms with patient preference study capabilities (MDIC website).

Additionally, it is important to engage appropriate statistical expertise for conducting the Bayesian decision analysis (BDA) approach, which is designed to develop a patient-centered statistical significance level threshold using PPI, if appropriate. While the MDIC-PD and MDIC-HF case study leaders worked with experts from Massachusetts Institute of Technology (MIT) and Quantitative Life Sciences (QLS) who designed a specific BDA model, with public dissemination of this approach (Chaudhuri, 2020), it should be possible in the future for a broader group of analysts to apply the BDA framework. A key learning from the case examples is the benefit of having the BDA statistical experts for the project embedded in the patient preference study team from the outset. While it is possible to bring this expertise in after the patient preference study conduct and analysis are complete, as was done in the MDIC-HF and Edwards examples, it is more efficient to approach the project seamlessly from the start, as was the case in the MDIC-PD study.

4.2.3 Engaging Regulators

An extremely important lesson from the case examples in this framework is the need to proactively engage with officials from CDRH from the beginning of any effort to develop PPI in support of medical device clinical trial design. CDRH has issued guidance documents for industry that support its interest in this type of approach and willingness to engage directly with sponsors in these initiatives (FDA CDRH website). CDRH's review staff, supported by staff with expertise in patient preference study design and interpretation, regularly works with sponsors to give feedback and guidance on the conduct of patient preference studies for use in regulatory evaluation (FDA, 2022).

FDA considers PPI as part of the totality of valid scientific evidence. PPI is not only valuable in the benefit-risk trade-off assessment but can be used throughout the medical product lifecycle from product ideation to clinical practice. FDA has explored the use of PPI in clinical trial design by collaborating to conduct a retrospective analysis of PPI in obesity-device studies (as described in the CDRH-Obesity case study). In addition, FDA staff

were active participants in both the MDIC-PD and MDIC-HF projects and are continuing to advance the use of PPI in clinical trial design in other therapeutic areas (FDA CDRH website). As more sponsors engage with regulators about the use of patient preference studies, the data resulting from these efforts are more likely to meet "valid scientific evidence" standards required for inclusion in regulatory processes.

4.2.4 Engaging Patient Advocacy Organizations and Patient Advisors

As a best practice, studies to develop PPI should include engagement with patient advocacy organizations (where they exist) and/or patient advisors who are living with the disease being studied and who can provide valuable early feedback on the design of the patient preference study, the assessment of the attributes of the disease and treatment that are important to patients, outreach efforts to engage participants, and analysis of the data. This early engagement can ensure that patient advocacy organizations feel connected to the process.

In the MDIC-PD patient preference study, project team members conducted multiple group discussions with the entire Michael J. Fox Foundation (MJFF) Patient Council and multiple interviews with a small group of volunteers from the MJFF Patient Council. Several people living with PD served as "patient scientists"[16] embedded in the research team.[17] This engagement helped ensure that the patient perspective was reflected in all study decisions, outcomes important to patients were measured, and the developed preference survey captured the attributes of the disease and its treatment that were relevant to patients. The patient preference survey was tested, refined, and finalized through an iterative pretesting interview process with 20 members of the MJFF patient community.

In the MDIC-HF case study, where organized patient advocacy among the patient population with HF is limited, the patient preference study team sought the input of patient advisors when developing the patient preference study. Given the demographics of the HF population (older, more comorbidities), this was a somewhat difficult undertaking. The MDIC-HF team also faced the challenge of having to recruit its patient preference study participants without an organized patient advocacy network to tap into. This is a scenario many device developers may face, given the myriad conditions treated with devices and the disparate patient populations they impact.

Overall, the MDIC-PD and MDIC-HF case examples underscore the importance of adapting the engagement strategy and approaches based on each project's specific needs when engaging patients to assist in developing and executing patient preference studies. Patient advisors do not need to be experts in the mechanics of a study; rather, patient preference study sponsors should ensure these individuals have the resources and training needed to be full participants in the project. In this way, it is possible to empower patients to truly impact the project rather than asking them to simply approve study materials and approaches. Additionally, when working with patients, it is important to be flexible regarding scheduling, logistics, and modes of communication, as patients are balancing their treatment, work, and family commitments. Finally, it is essential that results and outcomes from the patient preference study are communicated in lay terms and shared with the patients who contributed to the project.

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[16] This term is often used to describe an expert patient who participates in clinical study design teams to provide insights from the perspective of someone who is living with a condition or disease under study.

[17] Patient advisors in this project described their experience in an MDIC paper. *Incorporating Patient Perspectives in Clinical Trial Design and Research*. Accessed March 4, 2021. https://mdic.org/resource/incorporating-patient-perspectives-in-clinical-trial-design-and-research/

4.3 Developing PPI to Inform Clinical Trial Design

4.3.1 Selecting Attributes for the Patient Preference Study

A critical element of designing a patient preference study to inform the design of a medical device clinical trial is to select the most appropriate attributes that relate to safety and effectiveness (benefit-risk) endpoints in the clinical trial. As defined by MDIC's PCBR framework, a patient preference study attribute is an "[a]spect by which desirability or acceptability of medical interventions are evaluated in a preference survey. Attributes include types of benefits and risks associated with medical interventions" (MDIC website). This is especially true given that there is a limit on the number of attributes that can be tested within most types of patient preference studies (MDIC website, FDA CDRH website). Attributes are most relevant when they align with trial endpoints and are understandable to the patients who are asked to participate in the preference study.

If there is a specific type of device already in development for which PPI is sought, this will focus choices for the patient preference study attributes while there will be more clarity about the endpoints being evaluated. In the case of an ongoing pivotal study with regulatory intent, PPI may be most relevant to help identify what patients think about the benefit-risk trade-offs already defined in the clinical trial. In this case, the patient preference study could be conducted in parallel with the clinical trial or after the trial through labeling to help inform patients and providers about choosing the optimal therapy.

Conversely, if the goal is to evaluate patient preferences within a disease area (or subgroup of patients) without a specific type of device development program in mind or before a clinical trial has been designed (as was the case in both the MDIC-PD and MDIC-HF examples), then there can be flexibility in framing the patient preference study for a general type of device (e.g., neurostimulation for PD) without being tied to a specific set of technologies in development (although this can also complicate the effort). In the MDIC-PD example, a "bottom-up" approach was undertaken to leverage PPI to develop endpoints that would be meaningful to patients, without being limited by an existing endpoint already being evaluated for a certain device. By leveraging patient input from the patient advisors/patient scientists involved in the patient preference study, information about the importance of pain to patients with PD led to inclusion of Parkinson's-related pain as an attribute in the patient preference study. This could be used to support eventual use of pain as an endpoint in a future PD device development clinical trial.

In the MDIC-HF example, where six device manufacturers participated in the project, it was necessary to select broad attributes that could be relevant across various types of potential devices with the goal of identifying patient preference attributes that could inform a clinical trial endpoint. In this case study, patient preference data indicated that patients were more focused on improvements in their physical functioning, which would translate to improvements in their quality-of-life outcomes like functional status, than on clinically defined outcomes like hospitalizations, which have traditionally been incorporated as endpoints for clinical trials of HF interventions.

Regulatory Considerations

Sponsors should be aware of regulatory considerations and engage regulators in their decision-making about attribute selection for a patient preference study to ensure a clear, agreed-upon "crosswalk" from the patient preference study attributes to the endpoints in the clinical trial. This can be challenging, especially in instances where a traditional device clinical trial endpoint is a composite of multiple events, as is typical for HF studies. It is recognized that additional research is needed to create a crosswalk between PRO instruments, which reflect a composite of multiple items, and PPI attributes. Further methodological evaluation, perhaps through additional collaborations between The Professional Society for Health Economics and Outcomes Research (ISPOR) and FDA focused on devices (ISPOR website), would be a useful addition to the body of knowledge.

Identification of specific elements of a composite endpoint to define attributes for the patient preference study should be the subject of detailed discussions with regulators to align on the approach for evaluating and weighting measurable factors (often symptoms) that matter most to patients (Irony, 2017). Sponsors can use literature reviews, focus groups, or interviews with a small group of patients to identify which key factors are of importance. This information can then be leveraged to select attributes for a patient preference study to develop data that can support supplemental or alternative endpoints for the clinical trial. For example, a traditional endpoint in a mitral heart valve replacement clinical trial might be reappearance of mitral valve regurgitation, which is a clinically measurable condition of heart valve disease. While patient focus groups indicate they are often focused on their more immediate symptoms of the condition, which can include feeling tired or out of breath, than they are on their clinical presentation (American Heart Association website), clinical measures often have a relationship to patient symptoms. Sponsors should map out how the symptoms of the condition under study link to the clinically measurable conditions.

PPI can also be used to evaluate preference distinctions among different subgroups of patients to help structure clinical trial endpoints. For example, hierarchical endpoint analyses often count the "worst" outcome first (e.g., mortality). However, for some groups of patients, progressive Alzheimer's disease may be considered "worse" than death. (Johnson, 2019). In HF, for example, older patients may prefer a potential device without defibrillation to stop sudden death because they may not want to keep living with disabling HF. On the other hand, younger patients may want more time to live, even if that means living with HF.

Once attributes that matter to patients (including different subgroups of patients) have been identified through patient preference studies, sponsors can work with their clinical trial teams and regulators to incorporate and power them for endpoints in the clinical trial.

4.3.2 Recruitment of Representative Patients for the Patient Preference Study

4.3.2.1 Addressing Preference Heterogeneity

PPI can be extremely valuable in elucidating diverse perspectives among patients about risk tolerance, among other things. It is important to emphasize that diversity among different demographic groups (including diversity of experiences, clinical characteristics, and demographic characteristics) is distinct from diversity of preferences. It is important to avoid assuming that preferences among individuals within a certain demographic group or who share a similar experience or clinical characteristic will be similar. To that end, it may be useful to apply a latent-class approach, cohort analysis, or other approaches to analyze PPI that seek to discover relationships between patient characteristics (including preference heterogeneity) and the early adoption of new technologies.

A critical component of the process for developing PPI to inform clinical trial design is ensuring adequate recruitment (numbers and representativeness) within the patient preference study sample. A large enough sample size in the patient preference study may be needed to help understand preference heterogeneity within a disease population. This would allow for subgroup analyses that can elucidate distinctions in priorities and risk tolerances among different types of patients (e.g., severity of disease, symptoms, age, race, gender, socioeconomic status, early adoption of new technologies). To be confident that patient preferences identified through this process reflect the population under study (in terms of disease type, course of treatment, demographics, and risk tolerance), sponsors can intentionally plan to sample diverse patients as well as stratifying the sample after recruitment. If there is a particular subgroup of patients that is of interest, it may be useful to consider oversampling this group (greater than their representation in the target population) so that there is adequate statistical power to make comparisons with other subgroups or to generate preference weight estimates with greater precision.

4.3.2.2 Working With Patient Advocacy Organizations

As discussed earlier in this framework, engagement with patient advocacy groups can be an important approach to designing and conducting patient preference studies where possible. However, there are not always established patient groups for the disease or condition of interest (either because of the demographics and comorbidities of patients with a more common disease like HF, a physical disability requiring a device like a hip replacement, or a highly rare condition). In these cases, sponsors seeking to identify appropriate representation for a patient preference study will need to identify their own networks to engage with patients.

4.3.2.3 Engaging Clinical Sites and Online Platforms

While some individual clinical sites may have a demographically limited patient population based on geography and socioeconomic factors, many academic medical centers do serve diverse patient populations within their own institutions and through engagement with affiliated hospitals in their overall catchment area. Sponsors should consider the various trade-offs with using single or multiple clinical centers for recruitment of a patient preference study when developing PPI to inform the design of their clinical trial. Where required, engagement with local institutional review boards (IRBs) vs. a central IRB may be needed. It should be noted, however, that most survey research is now considered exempt from full ethics board review according to the updated Common Rule.[18] Sponsors are encouraged to contact the local IRB to ensure that the study complies with rules regarding the protection of human participants.

Online survey platforms with large patient panels, such as the Kantar Lightspeed platform (Kantar Lightspeed website) utilized in the MDIC-HF case study, provide the opportunity for rapid and wide outreach. In this example, online recruitment secured 500 participants for the patient preference study. A significant limitation of this approach in certain circumstances is its reliance on patients who self-report their disease (rather than those with a "confirmed diagnosis" who are referred by a clinician), a topic that is discussed in greater detail below. Additional limitations relate to frequent low rates of response to surveys and a greater likelihood that patients who participate in panels may often be younger and/or have milder medical conditions.

Provider referrals through a clinical center or network may provide additional confidence about the diagnosis of the patients who participate in the patient preference study. Additionally, this approach may be used to validate online participant cohorts and may also be the most successful in recruiting participants if the condition is rare. In some situations, it may make sense to recruit participants both through a clinical site and an online platform. For example, in the MDIC-HF study, 126 patients were recruited for participation from referrals within the Duke University Health System over a 3-month period (mid-April to mid-July 2020), and a large additional cohort of 500 participants was recruited over a 3-week recruitment period through an online platform.[19]

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[18] Category 2: Research that only includes interactions involving educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior (including visual or auditory recording) if at least one of the following criteria is met: (i.) The information obtained is recorded by the investigator in such a manner that the identity of the human subjects cannot readily be ascertained, directly or through identifiers linked to the subjects; (ii.) Any disclosure of the human subjects' responses outside the research would not reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, educational advancement, or reputation; or (iii.) The information obtained is recorded by the investigator in such a manner that the identity of the human subjects can readily be ascertained, directly or through identifiers linked to the subjects, and an IRB conducts a limited IRB review to make the determination required by .111(a)(7).

[19] It should be noted that the period during which participants were recruited from Duke occurred during the COVID-19 pandemic.

4.3.2.4 Confirmed Diagnosis vs. Self-Report

To ensure that PPI is reflective of the intended population for a potential medical device, it is important to be as confident as possible that the participants in the patient preference study accurately reflect the population with the disease or condition under study.

The issue of how to recruit those patients for the patient preference study in a timely and cost-effective way relates to the reliability of the reporting by and about the patients from whom PPI is generated. For many diseases, this is not always as obvious as it sounds, especially when there are subtypes of disease, specific aspects, or stages of the diagnosis. Not all patients are sure about the specifics of their condition. For this reason, a frequent approach is to engage patients who have been referred by a physician or whose electronic medical record includes the specific diagnosis that the device under development is intended to treat. This is often referred to as a "confirmed diagnosis."

Because these methods can be time consuming, costly, and are often limiting factors to rapid recruitment, patient preference studies may also incorporate input from patients who "self-report" or self-identify that they have a certain condition. In these cases, the study sponsors may want to look for secondary data (e.g., the channel through which a patient was contacted, such as a patient organization network) and supporting information from participants (e.g., information about their symptoms or treatments) that can be used to increase confidence about the diagnosis.

In the MDIC-PD, MDIC-HF, and Edwards examples, multiple approaches were used to recruit the patient preference study with a mixture of "confirmed diagnosis" (based on physician referral or documented diagnoses in medical records) patients and those who self-reported their diagnosis (recruited via a commercial web vendor or patient advocacy group). The intention of this type of hybrid approach was to engage larger numbers of participants receiving medical care across a broader range of providers and locations and to compare preferences between individuals recruited from different sources. Ultimately, the goal was to test whether potentially faster and less costly approaches to recruitment could substitute or complement data collected from clinical sites. If it were found that PPI using data collected from different recruitment sources generated similar results, researchers could address potential concerns about the generalizability of study PPI results. If it were found that preferences differed between sources with confirmed vs. self-reported conditions, investigation as to why preferences differed would be warranted.

In the MDIC-HF example, the results from the confirmed diagnosis patients were compared with those received from the self-report group through the online panel, leading to the conclusion that there were not significant differences between the two groups, allowing for pooling of data from all respondents.

This approach may not work in all situations, and it should be noted that the PPI generated from the two MDIC case examples discussed in this framework has not yet been applied in a regulatory context.

4.3.3 Leveraging a Bayesian Decision Analysis Framework

With the advent of innovative clinical trial designs and new approaches for data analysis, device developers have been exploring ways to leverage PPI to inform trial design, with an increasing focus on PPI's impact on statistical considerations. Models to improve clinical trial design propose using PPI to balance the urgency of need for new therapeutic options against risks posed by those therapies by adjusting sample size and statistical significance thresholds to reflect patient preferences (Isakov et al., 2019; Chaudhuri et al., 2018; Montazerhodjat, 2017).

Quantitative PPI can be used to determine the size of the benefit that is required to demonstrate success in a clinical trial for a given therapy's risk profile (Montazerhodjat and Lo, 2015; Ho et al., 2015; Hauber et al., 2013). Additionally, PPI can inform the target sample size needed to deliver statistical accuracy (in the form of what level of statistical alpha [α], or type 1 error, is considered acceptable by statisticians and clinical investigators).

Experts in health economics have been researching statistical approaches to quantitatively link patient preference information to levels of uncertainty. In their 2017 paper about a Bayesian approach to decision analysis in oncology clinical trials, Montazerhodjat et al. suggested that traditional adherence to an arbitrarily set significance level threshold creates an ethical dilemma. They noted that patients with a serious or terminal illness may prefer to accept a greater likelihood of endorsing an ineffective therapy, even if the likelihood of an effective therapy is small (Montazerhodjat et al., 2017).

A Bayesian decision analysis (BDA) framework has been proposed and utilized as a methodology to develop patient-centered significance level thresholds by incorporating PPI into the selection of the critical uncertainty cutoff point (Montazerhodjat et al., 2017; Chaudhuri et al., 2018; Isakov et al., 2019). The BDA framework provides a systematic, quantitative, and transparent approach to setting the statistical significance threshold for a clinical trial such that the overall consequences of approving an ineffective and possibly harmful treatment (false approval or type I statistical error) are balanced against the consequences of rejecting an effective treatment (false rejection or type 2 statistical error) using insights gathered from the patient population under study. The BDA framework provides insight into ways that large clinical trials, while developing significant amounts of evidence, could unnecessarily delay patient access to effective treatments and result in failure to approve a device that could be acceptable for use in a subset of patients with a given disease.

Understanding patient preferences may provide an approach to allowing clinical trials to proceed more quickly if sponsors leverage PPI to consider patients' urgency and risk tolerance and identify patients who are willing to take a greater risk for the possibility of a greater benefit. In this way, it may be possible to reduce target sample sizes for a premarket trial. This might be particularly valuable in diseases for which clinical trial recruitment can be challenging (FDA CDRH website).

It may be possible to use the BDA framework to weigh trade-offs, by applying the perspectives of patients, clinicians, and regulators in calculating the optimal significance level, making it a potentially valuable tool for facilitating the clinical study design process. However, to date, the uptake of this approach by manufacturers and trialists has been quite limited. One barrier is the lack of existing, high quality, relevant patient preference data. There is continuing need to conduct and publicly report PPI studies to further develop the landscape of existing high-quality data that can be used to support these approaches.

4.3.4 Statistical Significance and *P* Values

A key statistical concept in clinical studies for medical products is to minimize the possibility that the observed results could have occurred by chance. A small *P* value means that an outcome at least as extreme as the observed outcome of a clinical trial result (e.g., the effectiveness of the product being assessed) would be unlikely to occur under the null hypothesis (e.g., the hypothesis that the product being assessed is no different from the control group).

In a formal significance test, the null hypothesis is rejected if the *P* value of a clinical trial result falls below a fixed, predefined threshold value α, which is referred to as the significance level. Historically, for clinical trials, a two-sided significance level of 5% (or one-sided 2.5%) has conventionally been used to determine whether a result is statistically significant. While convenient as a cutoff point, this threshold is not tied to any context. Indeed, the American Statistical Association released a statement on *P* values in which they stated: "A *P* value, or statistical significance, does not measure the size of an effect or the importance of a result" (Wasserstein, 2016).

Use of a fixed threshold across all clinical trials assumes that all patients have the same tolerance for uncertainty, or for the trade-off between the risk of endorsing an ineffective therapy (type I statistical error) and the risk of rejecting an effective therapy (type II statistical errors) (Montazerhodjat, 2017). However, this convention does not fully take into consideration the needs of the patient population, the clinical importance of a result, or the potential impact on public

health. For example, some patients who are more risk tolerant may regard evidence with $P<0.1$ for the statistical significance of evidence related to the efficacy of a potential new therapy as sufficient. Other patients may be more conservative, requiring greater certainty with respect to the evidence. The amount of uncertainty that a patient is willing to accept may be driven by several factors, including the severity of disease, quality of life, and access to alternative options.[20]

In considering uncertainty in benefit-risk determinations, FDA considers several factors, as appropriate to the circumstances, including "patients' perspective on appropriate uncertainty about the probable benefits and risks of the device, if available" (FDA Guidance, 2019).

In the context of clinical trials, patient perspectives could be considered when setting significance level thresholds[21] according to the unique factors affecting the community and the patient group being studied (i.e., at the population level; **Figure 6**).

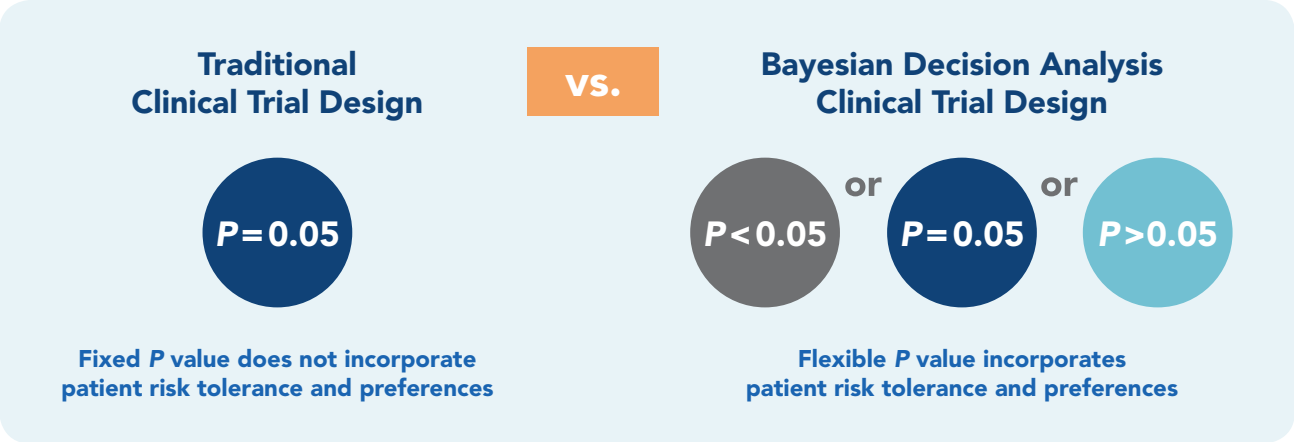

Figure 6. Comparing traditional and Bayesian decision analysis approaches for setting significance levels in clinical trial design.

The MDIC-PD, MDIC-HF, and CDRH-Obesity examples demonstrate how this can be accomplished through a BDA approach that first recognizes patients within the same disease group may have different tolerance for risk and then weighs and stratifies them accordingly. A BDA model can generate summary statistical considerations that encapsulate a significant volume of detailed data stemming from a robust patient preference study. The result may provide an opportunity to support a regulatory strategy in which a device with a higher level of risk may still be approved for use by a subgroup of patients (**Figure 6**).

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[20] The classical clinical trial endpoint analysis for a safety endpoint or an effectiveness endpoint is fundamentally one-dimensional. While useful for statutory purposes ("reasonable assurance of safety and effectiveness") and for device-device comparisons, it is less useful for evaluating the benefit-risk trade-offs fundamental to PPI analytics. On the other hand, "net benefit" outcome endpoints are generally discouraged due to implicit ambiguities of weighting. The Bayesian decision analysis framework described in this section bridges these two approaches, enabling the classical clinical trial endpoint analysis to reflect multidimensional benefit-risk trade-offs.

[21] The significance threshold is chosen during the planning of an A/B test, and it corresponds to the probability of committing a type I error (registering a false positive), which is deemed acceptable under the specific circumstances of the test in question.

In the MDIC-HF example, surveys of patients with HF, such as the one used in this analysis, asked respondents to choose between the current standard of care vs. other hypothetical treatments. This effort helped to determine the strength of patient preferences among the surveyed patients, information which can then serve as one of several inputs to help inform the regulatory decision-making process.

In addition to incorporating PPI related to risk tolerance among patients, the BDA framework can also evaluate trade-offs relating to time preferences among patients (e.g., how long would patients be willing to wait for a novel device). This is relevant given the length of time it can take to complete a large trial. Patients with a serious condition, rapid progression, and lack of effective therapy or standard of care may be willing to accept more uncertainty about the likely benefit and risk of a new device in exchange for accessing it sooner. In this case, it may be possible to design a clinical trial that incorporates higher levels of uncertainty and conduct it enrolling fewer patients over a shorter time frame.

4.4 Communicating the Effort

It is important to clearly communicate to all stakeholders why and how decisions about a clinical trial's design were made based on PPI. Regulators, clinicians, patients, payers, and patient advocates need to understand what assumptions have been made in the design of a specific clinical trial and how certain analysis models have been applied. For example, if a clinical trial is powered for certain subgroups of patients based upon their risk tolerance as derived from PPI, this point should be clearly presented in the regulatory process, labeling, and other communications about the device. In the MDIC-PD case example, a summary of the results was developed for the patient community with PD to be shared through the MJFF and its network.

If the clinical trial design sets the significance level higher than the traditional one-sided 2.5% for the endpoint assessment, clarifying that the level was informed by the PPI study may be important. The clinical trial sponsor should also be prepared for the possibility that the BDA framework could result in setting a significance level lower than the traditional level (less than $\alpha=0.05$), which would result in an increased sample size.[22]

Once a device is approved, it is important for healthcare providers and patients to have information about its value, including how it addresses the things that matter most to patients, as identified through patient preference studies.

[22] Some examples of this situation are given by Montazerhodjat, *JAMA Oncol.* 2017;3(9):e170123.

SECTION 5

Conclusion

Investigators, device manufacturers, regulators, payers, patient advocates, and patients share the common goal of streamlining development of better, safer medical products that can improve outcomes for an array of serious diseases and conditions. A rigorous clinical trial process is the central requirement for developing the evidence needed to ensure that a new device can be safe and effective. Some stakeholders suggest that patient preferences within a disease community may not align with traditional clinical outcome measures and can vary widely based on a variety of factors. Most stakeholders in the medical device ecosystem agree, however, that patient preference and clinical outcome measures should not be viewed as either/or but rather as an area where important work needs to be done to align and integrate the two using reliable methods and sufficient basis for generalizability to the population under consideration. For this reason, development of robust quantitative tools such as patient preference studies and BDA models offers the opportunity for sponsors and regulators to seek ways to better evaluate what matters most to patients (patient values) in the product development and regulatory review processes (ISPOR, 2020).

By conducting two detailed case study example projects, MDIC sought to identify key aspects of these approaches that may be most relevant to decision-making by device developers. These projects point to important lessons and considerations, including key aspects of setting up a patient preference study for the purpose of informing clinical trial design, selection of appropriate attributes to measure in the patient preference study, and engaging with the patient community and regulatory officials from the beginning and throughout the effort.

SECTION 6

Future Directions

More work is needed to further expand these efforts, including device-specific projects that tie directly to a clinical development program and subsequent regulatory review. Other topics that require significant additional work include expanding techniques for the conduct of patient preference studies to enhance diversity of patient perspectives and incorporate all voices into the process of developing PPI. It is also important to consider bringing these topics into future discussions with payers about incorporating PPI in their decision-making about coverage and reimbursement.

A key consideration for clinical development teams within sponsor organizations is understanding the trade-off between costs and benefits for developing and implementing PPI within their clinical trial design efforts. Additional evidence will be needed to demonstrate the value of this approach overall.

Including the acquisition of PPI within a trial or in parallel and having the plan prospectively incorporated into the clinical trial statistical analysis plan (SAP) to corroborate clinical assumptions used to design the trial may be highly beneficial. Additional evaluation is needed for the best approaches when PPI is not available to a sponsor in the pre-IDE time frame. Is there an alternative route that could allow collection and incorporation of PPI after a clinical trial has begun? Leveraging adaptive trial/study design might be an option in this case and would benefit from further consideration. For example, for a given significance level and statistical power determined from the severity of the adverse effects of type I and type II errors on the patient, stopping boundaries for superiority and futility for the primary endpoint could be designed. This protocol would allow the trial to end early in cases where the investigational treatment shows clear signs of effectiveness or ineffectiveness for the patient, or to collect additional observations when current observations do not lead to a clear choice.

In the future, PPI might be used to inform the statistical analysis plan after the study has been initiated and before the clinical data are analyzed for regulatory submission. If a patient preference study reveals higher than expected thresholds or tolerance for risk of a certain outcome, it may be possible to approach FDA with a proposal to modify the planned statistical analysis so that it matches more closely with the preference data. For example, in a case where "success" is measured by a patient response such as improved function, the study design might require a certain improvement for success, but the PPI may reveal that a much smaller improvement is acceptable to the patients. In these situations, the FDA will likely expect to be informed of this possibility in advance.

With increasing published information about patient preference studies and BDA models, more clinical trial sponsors and teams will have the opportunity to incorporate learnings in their development programs. As the body of evidence supporting the feasibility of these approaches grows, all stakeholders will develop additional confidence and comfort with using PPI to design the most streamlined and efficient clinical trials possible in the development of medical devices, yielding outcomes that systematically include the benefit-risk preferences of patients.

Section 7: Glossary

SECTION 7

Glossary

ADAPTIVE DESIGN CLINICAL TRIALS	A clinical trial design that allows modifications to the trial and/or statistical procedures after its initiation without compromising its validity and integrity. Adaptive trials often use the accumulation of past observations to modify their progress.
ALTERNATIVE HYPOTHESIS	In a statistical test, the hypothesis that there is a true difference between specified populations. In clinical trials, the true difference represents a clinically important difference.
ATTRIBUTE	An aspect by which desirability or acceptability of medical interventions are evaluated in a preference survey. Attributes include types of benefits and risks associated with medical interventions.
BAYESIAN DECISION ANALYSIS (BDA)	A Bayesian approach strikes the optimal balance between type I and II errors and, in certain cases such as diseases with unmet medical needs, leads to expedited approval decisions with smaller patient sample sizes and tolerable type I error rates higher than 5%. Type I and II errors are assigned different costs, considering balance between the costs associated with the use of an inferior treatment during and after the trial. Given these costs, other population parameters, and prior probabilities, it is possible to compute an expected cost for any fixed-sample clinical trial and minimize the expected cost over all fixed-sample tests to yield the BDA-optimal fixed-sample trial design.
COMPOSITE ENDPOINT	A composite endpoint consists of at least two or more distinct endpoints, called component endpoints. Because of the need to observe a certain number of primary endpoints to achieve adequate statistical power for a study, investigators opt to use component endpoints that contribute to an overall composite event rate.
CONFIRMED DIAGNOSIS	Study participant identified as having the specific condition under study through physician referral or electronic medical record.
DISCRETE CHOICE EXPERIMENT	An experiment that asks respondents to state their choice among sets of hypothetical alternatives. Each alternative is described by several characteristics, known as attributes, and responses are used to infer the value placed on each attribute.
LATENT CLASS ANALYSIS	Model-based clustering approach used to detect choice patterns given the attributes in a choice experiment. In latent-class analysis, survey respondents are grouped probabilistically into a prespecified number of classes, and average preference estimates are obtained for each class. Respondent characteristics can be jointly modeled with class-specific attribute preferences to identify individual characteristics that are significantly associated with class-membership probabilities.

NULL HYPOTHESIS	In a statistical test, the hypothesis that there is no significant difference between specified populations, any observed difference being due to sampling or experimental error.
***P* VALUE**	In statistics, the *P* value is the probability of obtaining results as extreme as the observed results of a statistical hypothesis test, assuming that the null hypothesis is correct. A smaller *P* value means that there is stronger evidence in favor of the alternative hypothesis.
PATIENT PREFERENCE INFORMATION (PPI)	Qualitative or quantitative assessments of the relative desirability or acceptability to patients of specified alternatives or choices among outcomes or other attributes that differ among alternative health interventions.
PATIENT PREFERENCE STUDY	A survey that asks patients to choose between different treatment options and measures their preferences in a standardized and quantitative manner.
PATIENT SCIENTIST	Term used to describe an expert patient who participates in study design teams to provide insights from the perspective of someone who is living with a condition or disease under study.
SELF-REPORT DIAGNOSIS	Study participant self-identified as having the specific condition under study.
THRESHOLD TECHNIQUE	Method that determines the maximal change in one attribute respondents are willing to accept to achieve a given change in another attribute.
TYPE I ERROR/TYPE II ERROR	Type I error is the rejection of a true null hypothesis (also known as a "false-positive" finding or conclusion; example: "an innocent person is convicted"), while a type II error is the non-rejection of a false null hypothesis (also known as a "false-negative" finding or conclusion). In statistical hypothesis testing, a test's significance level, denoted by α, is the probability of type I error when the null hypothesis is true. On the other hand, the power of a hypothesis test, denoted by $1-\beta$, is the probability of avoiding a type II error when a specific alternative hypothesis is true.
UNCERTAINTY ATTITUDE	Uncertainty attitude reflects the degree to which uncertainty in the attributes of a treatment alters one's decisions about use of the treatment.

Section 8: Appendices

SECTION 8

Appendices

Appendix A: MDIC Patient-Centered Outcomes Research Project for Parkinson's Disease (MDIC-PD)

The Patient-Centered Outcomes Research (PCOR) project encompassed nearly two years of collaboration among the Medical Device Innovation Consortium (MDIC), the Michael J. Fox Foundation for Parkinson's Research (MJFF), Center for Devices and Radiological Health (CDRH), Massachusetts Institute of Technology (MIT), and RTI Health Solutions and focused on investigating how the preferences of patients with Parkinson's disease (PD) could be used to set statistical significance levels in clinical trial design (MDIC website).

MDIC selected PD for this project because it is a chronic, degenerative condition with few good treatment options. The patient population with PD is heterogenous in terms of the lived experience of the disease, presenting with a wide variety of symptoms, severity, and speed of progression. This heterogeneity makes it difficult to recruit enough patients to satisfy the statistical requirements of traditional clinical trial designs, suggesting that traditional statistical requirements may be unnecessarily lengthening the timeline for development of promising therapies for certain patient populations. For these reasons, PD was a useful test case for exploring the most important benefits and risks to patients and developing a model to design clinical trials based on disease-specific patient preferences (MDIC website).

The objectives of the MDIC-PD project were to develop and test a method of determining appropriate trial size and statistical significance levels for PD clinical trials based on patients' risk tolerance. While this project focused on a hypothetical medical device clinical trial within a specific disease area, its overarching goal was to demonstrate how to employ a method that may be generalizable to other diseases (especially serious, chronic, or debilitating conditions with limited treatment options), optimizing clinical trial design to benefit patients.

The MDIC-PD project engaged clinical experts, regulators, methods experts, and patients throughout all study stages. The effort began with qualitative research that incorporated input from patient partners (identified with MJFF) and regulatory end users to identify and prioritize outcomes (attributes) important in the treatment of PD (Benz, 2021). This effort identified benefits, risks, and other considerations that are meaningful and relevant for patients with PD. Twelve common clinical effectiveness endpoints (benefits of treatment) and 26 safety endpoints (risks of treatment or adverse events) were identified and then prioritized by a group of patients with PD (selected in conjunction with the MJFF and its Patient Council). The top priorities were then used to select "attributes"[23] for the patient preference study (characteristics of a hypothetical PD treatment relating to benefit and risk that would be presented to the patient preference survey respondents). In addition to symptoms and risks, reductions in prescription drug dosage were included, as was "time until treatment availability," which measures patients' tolerance for waiting for a potential new treatment that may be delayed by research and development, clinical trial, or regulatory processes.

The prioritized attributes were incorporated into an online patient preference survey for patients with PD designed to quantify the maximum levels of risks patients would accept for benefit using 20 possible benefit-risk pairs (comprising four benefit options, four risk options, and a separate option relating to wait time for development of a new therapy) of a hypothetical neurostimulation device (Hauber, 2021).

[23] Attributes are "aspects by which desirability or acceptability of medical interventions are evaluated in a preference survey. Attributes include types of benefits and risks associated with medical interventions." MDIC, PCBR (MDIC website).

The stated preference method known as "threshold technique"[24] was used to quantify patients' risk tolerance for new or worsening depression or anxiety, brain bleed, or death in exchange for improvements in "on-time," motor symptoms, pain, cognition, and pill burden. The survey elicited patients' maximum willingness to wait to receive treatment benefit.

Regression analysis of the data from the patient preference study was conducted to develop estimates of maximum acceptable risk (MAR) and maximum acceptable wait time for different levels and types of treatment benefits. These results were then used in a Bayesian decision analysis (BDA) model to develop information about optimal trial design for a potential PD device, leveraging patient insights in a rigorous statistical framework. For patients who had previously received deep brain stimulation (DBS) treatment, the significance levels identified by the BDA framework were similar to or larger than 0.05, while for patients who had never received DBS, the significance levels were smaller than 0.05. Moreover, in both these populations, the patients with more severe cognitive and motor function symptoms were willing to accept more uncertainty. While this approach yielded the conclusion that patients with PD are willing to accept substantial risks to improve symptoms, preferences are diverse given the heterogeneity of the patient population with PD and the range of treatment benefit.

The final step in the MDIC-PD project was to quantify the loss of value to public health associated with false approvals and rejections, then apply BDA to determine the optimal significance level and sample size that minimize this loss and maximize this value. This approach allowed modification of the traditional 0.05 significance level used in standard randomized clinical trial (RCT) designs to better reflect patient preferences and their medical needs. Specifically, the MDIC-PD project found that patients with severe symptoms and prior experience with DBS described loss of value from larger, lengthier clinical trials that are focused on severely limiting type 1 error. In these cases, a missed opportunity to approve a beneficial yet more risky treatment has a substantial negative impact on risk-tolerant patients. On the other hand, more risk averse patients (such as those with relatively mild symptoms), require clear demonstration of clinical effectiveness (and a more stringent significance threshold) to reduce the probability of a false approval and potential harm from an approved device.

[24] While this approach is similar to a discrete choice experiment (DCE), under the threshold technique, the level of one attribute at a time is varied until the threshold level of that attribute is determined. In the patient with PD preference study, each option was defined by one or more treatment benefits and one or more treatment-related burdens (i.e., a risk of harm and/or wait time). The first treatment, referred to as the reference treatment, represented no treatment, standard of care, or the patient's current treatment. The second treatment, referred to as the target treatment, represented an alternative to the reference treatment. The level of benefit (burden) at which a patient switches his or her choice represented the threshold level of benefit (burden) that exactly offset the treatment burden (benefit) for that patient (Hauber and Coulter, 2020).

Appendix B: MDIC Heart Failure Project (MDIC-HF)

This effort, which involved six medical device companies supportive of learning more about patient preferences in the treatment of heart failure (HF), focused on developing and conducting a patient preference study aimed at understanding patient preferences for features relevant to various HF interventions. The primary study objective was to apply best-practice stated-preference methods to quantify patients with HF willingness to accept therapeutic risks in exchange for improved effectiveness of devices used to manage HF (MDIC website).

Respondents were presented with a status quo, or "no device" scenario, represented by a health trajectory representing a patient expected to live three years with physical functioning and symptoms equivalent to New York Heart Association (NYHA) class III, followed by two years with functioning and symptoms equivalent to NYHA class IV. The patients were also expected to be treated with guideline-directed therapies including drugs and/or devices. Device effectiveness was framed as a one-year improvement from NYHA class III to NYHA class II and/or an extended one-year duration of functioning equivalent to NYHA class III and associated extended survival. The first risk attribute presented as an unequivocally severe adverse event upon which to evaluate risk tolerance was risk of device-associated 30-day mortality. The second risk attribute represented a collection of potential for a two-day hospital complication related to device use that could occur to account for various potential adverse events. The study also included the option of a device that could be adjusted remotely (Reed, 2021). Whereas many patient preference studies use a specific risk or adverse event to measure risk tolerance, in this study, device-associated risks were represented as a group of potential complications that could occur. This approach facilitated application of the study results across different types of devices to be more reflective of clinical and regulatory decision-making in which the cumulative risk of various types of clinical complications that could occur (Reed, 2021).

Participants for the MDIC-HF patient preference study were identified through an online research platform (Kantar Lightspeed)[25] and through the Duke University Health System (DUHS). The patient preference study was conducted using a stated-preference survey instrument that included a discrete choice experiment (DCE) design. This approach was selected to estimate metrics that are directly relevant to benefit-risk decisions such as maximum acceptable risk (MAR) for a given benefit and "minimally acceptable benefit" (for a given risk).

In the DCE for the MDIC-HF project, respondents were asked to select their preferred treatment alternatives in a series of experimentally controlled pairs of hypothetical devices and a "no device" alternative. The devices were defined by effectiveness (years with physical functioning equivalent to NYHA class[26] II, III, and IV) and treatment-related risks of adverse events, which included a risk of death and risk of device-associated complications, along with a feature representing whether the device can be adjusted remotely.

The patient preference survey also included questions probing respondents' demographic characteristics and their experience with HF and treatment, as well as questions testing whether respondents comprehended the information presented to them in the survey instrument.

Data from the survey were analyzed using a random-parameters logit model with dummy-coded variables for all levels in each attribute. Scale-adjusted models were used to compare preferences and estimates of MARs for multiple subgroups of respondents, including age, gender, NYHA class, previous device, time since diagnosis, and ejection

[25] Kantar Research Services website. Accessed September 30, 2021. www.Lightspeedresearch.com

[26] Doctors usually classify patients' heart failure according to the severity of their symptoms. The New York Heart Association (NYHA) Functional Classification places patients in one of four categories based on how much they are limited during physical activity. American Heart Association website. Accessed March 4, 2021. https://www.heart.org/en/health-topics/heart-failure/what-is-heart-failure/classes-of-heart-failure

fraction (where available). In addition, latent-class analyses were conducted to evaluate the prevalence of groups with different preference patterns.

Findings from the latent-class analysis indicated that most patients with HF were willing to accept single-digit risks of mortality for one-year gains in survival over which their physical functioning would be stable or would improve. For these health gains, most patients were generally tolerant of in-hospital, two-day complication risks that would occur as frequently as one in four to one in five patients. While the more risk-averse group still was willing to accept up to 2% mortality and double-digit in-hospital 2-day complication rates, about 1 out of 5 patients were generally less risk tolerant for improvements in functioning and survival consistent with the scenarios shown in this survey. In all, these results underscore the need for providers and patients to engage in shared decision-making to ensure that each patient's preferences are considered prior to the receipt of an elective medical device (Reed, 2021).

The findings from the MDIC-HF patient preference study were used within a Bayesian decision analysis (BDA) framework to support input to future trial design and regulatory engagement. The BDA model used the benefit-risk preferences to estimate the value lost from a patient perspective of making an incorrect regulatory decision. For example, in the case of a false approval, the new therapy was assumed to provide no benefits relative to the standard of care but would contain additional risk in the form of adverse events such as death or complications. On the other hand, an incorrect failure to approve (a false rejection) results in the missed opportunity to receive a therapy that is more effective than the standard of care.

Multiplying these costs by their probabilities and summing across the various scenarios result in the expected loss of an incorrect regulatory decision. The BDA framework was then used to determine the optimal statistical significance threshold such that the expected harm of these downside scenarios is minimized. The interactive Quantitative Life Sciences (QLS) BDA tool illustrates how the optimal statistical significance threshold changes as a function of the cost of false approval and false rejection, as determined by the patient with HF preference information.

For the MDIC-HF case study, the BDA-optimal one-sided significance threshold for the hypothetical trial was estimated to be 3.2%, greater than the threshold value of the standard design of 2.5%. This result reflects the willingness of these patients to bear additional uncertainty regarding the effectiveness of the investigational device (i.e., the additional duration of functional equivalence to NYHA III) to reduce the chance of missing its benefits.

Using the patient preferences for the more risk-tolerant subgroup of patients, which among other characteristics tends to include patients who previously received a cardiac device, the BDA-optimal one-sided significance threshold for the hypothetical trial was estimated to be 9.4%, which is almost 4 times the standard threshold of 2.5%. For patients with prior experience with cardiac devices, value is lost due to clinical trials that are too conservative about their false approval rate. Here, a missed opportunity to approve a potentially beneficial yet more risky treatment has a substantial negative impact on risk-tolerant patients.

Finally, for risk-averse patients, such as those with no previous cardiac device experience, the traditional significance level of 2.5% is more permissive than the calculated patient-centered thresholds. Indeed, given the baseline estimates used in the case study, the investigational device was not preferred to the control treatment even under the alternative hypothesis. In these cases, patients require clear demonstration of clinical effectiveness to reduce the probability of a false approval and subsequent harm to their health.

Appendix C: Precursor Heart Failure Study (Abbott Heart Failure)

In support of device development programs for a transcatheter mitral valve repair device for patients with heart failure (HF) and symptomatic secondary mitral regurgitation, in 2017, a patient preference study was launched by Abbott[27] to provide quantitative patient preference evidence on benefit-risk trade-offs (Reed, 2019). The study employed a discrete choice experiment (DCE) survey to quantify patients' tolerance for 30-day mortality or serious bleeding risks to achieve improvements in physical functioning or reductions in HF hospitalizations.

The patient preference survey evaluated four attributes: physical functioning, number of HF hospitalizations over 2 years, and 30-day risks of dying and of severe bleeding. Respondents were recruited via an online panel and through the Duke University Health System (DUHS). Random-effects logit regression was used to model treatment choices as a function of benefit and risk levels. Results of this patient preference information (PPI) study indicate that severity of HF symptoms influences patients' willingness to accept risks associated with mitral valve medical devices.

A key finding of this effort relates directly to clinical trial design, specifically selection of endpoints. While most clinical studies for HF therapy use hospitalization or repeat hospitalization as an endpoint, the PPI from this study suggests that an endpoint relating to number of hospitalizations on its own is not what matters most to patients. Rather, when accounting for number of HF hospitalizations, patients are more focused on their everyday physical functioning.

[27] Reed SD, Fairchild AO, Johnson FR, et al. Patients' willingness to accept mitral valve procedure-associated risks varies across severity of heart failure symptoms. *Circ Cardiovasc Interv.* 2019;12(12):e008051. Accessed March 17, 2021. https://www.ahajournals.org/doi/10.1161/CIRCINTERVENTIONS.119.008051

Appendix D: Mitral Valve Regurgitation Patient Preference Study (Edwards)

In April of 2020, Edwards Lifesciences[28] completed a discrete choice experiment patient preference information (DCE PPI) study to quantify the maximum level of risk that patients would accept to achieve different potential benefits of a mitral valve regurgitation (MR) repair device. This study aimed to gain an understanding of patients' preferences for the benefits and risks of procedures to treat MR, particularly treatment attributes associated with mitral valve repair via a minimally invasive surgical treatment profile vs. open-heart surgery.

The online DCE PPI survey was developed based on a targeted literature review and input from clinical experts (cardiothoracic surgeons) and patients, including a qualitative study of patient perspectives. A draft DCE PPI survey was pretested with patients with MR (n=10) and updated to reflect their feedback. The final DCE PPI included 6 attributes: procedure invasiveness, procedure recovery, 2-year risk that MR symptoms reappear, 2-year risk of reintervention, 30-day risk of disabling stroke, and 30-day risk of new-onset atrial fibrillation. All attributes were clinically relevant, reflected clinical study outcomes related to mitral valve repair procedures, and incorporated qualitative feedback on attribute descriptions to maximize patient comprehension and minimize risk.

The design included 24 paired comparisons (choice tasks) divided into 3 blocks, with each participant randomly assigned to 1 block (such that each participant completed 8 experimental choice tasks). Two additional choice tasks, a dominance test and a holdout task, were presented for a total of 10 choice tasks per participant.

The final analytic sample size was 118 adult patients with MR living in the United States. Two cohorts were recruited: patients with a clinically confirmed diagnosis (n=30) referred by cardiovascular clinics and patients with a self-reported diagnosis (n=88) referred by email invitation from multiple online databases.

Preference estimates were used to calculate relative attribute importance (RAI), maximum acceptable risk (MAR), and predicted choice probabilities for attribute level differences and treatment profiles approximating the choice between a minimally invasive surgical treatment profile and open-heart surgery-like profile. Specifically, the relative importance of each attribute was calculated in terms of the difference in levels between the two treatment profiles. Benefit-risk tolerance thresholds were estimated as the maximum increased risks of failed efficacy/durability (defined separately as symptom recurrence and reintervention) participants were willing to accept in exchange for the benefits associated with the minimally invasive (relative to "open-heart surgery-like") treatment profile.

The study provided valuable new quantitative information on patients' benefit-risk perspectives for treatment of MR by mitral valve repair. In summary, participants showed distinct preferences among the attributes included in the DCE PPI, with all preferences in the expected directions. All attributes were important in making treatment choices.

More specifically, this DCE PPI study demonstrated that the target patient population was willing to tolerate a 22.6% increased risk of reintervention within 2 years or a 34.6% increased risk that symptoms related to recurrent MR reappearing within 2 years, in exchange for the potential benefits and risks of a minimally invasive alternative to open-heart surgery.

Furthermore, the BDA framework, a method for incorporating PPI as an explicit means to set significance levels in clinical trial designs, was applied to the estimated patient preference model from the mitral valve DCE PPI study, formulating a patient-centered, fixed-sample trial design for the clinical study being conducted to support regulatory approval.

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[28] Edwards Lifesciences. Accessed March 4, 2021. https://www.edwards.com/

The Bayesian decision analysis (BDA)-optimal one-sided significance threshold for the clinical trial was estimated to be 3.8%, which is 52% greater than the value of the standard design of 2.5%. In this case, value could be lost when a trial design is too conservative regarding the false approval rate. Here, a missed opportunity to approve a potentially safer yet similarly effective treatment has a substantial negative impact on patients with MR. These patients were willing to bear additional uncertainty regarding the effectiveness of the minimally invasive alternative (i.e., the risk that MR symptoms reappear and the risk that a reintervention is required) in order to reduce the chance of missing out on potential safety benefits (i.e., a less invasive surgery with a shorter recovery period, and a decreased risk of stroke and new-onset atrial fibrillation).

Finally, the BDA framework was used to identify the BDA-optimal non-inferiority margin for the clinical trial from the patient perspective by using the one-sided significance threshold of 2.5%; when this was done, the optimal non-inferiority margin that maximizes expected patient value was 21.6%. This is comparable with the prespecified non-inferiority margin of 20.0% used in clinical study design to test the primary effectiveness endpoint and suggested this margin was well calibrated as clinically significant from the patient perspective.

The results from the PPI study provide sufficient evidence that, on average, patients would be willing to accept certain estimated risks of lower efficacy/durability associated with a minimally invasive alternative to open-heart surgery, and a majority would accept the potential risks in exchange for its benefits.

Findings from the PPI study and BDA model were accepted by FDA/Center for Devices and Radiological Health (CDRH) in Edwards' investigational device exemption (IDE) supplement application to address the Agency's request for clinical justification of a 20% non-inferiority margin in a clinical study to support regulatory approval of an investigational device. This example was one of the first publicly known examples of FDA/CDRH accepting patient preference data to help support the rationale of a clinical trial design, giving patients a meaningful and important voice in the medical device lifecycle.

Appendix E: CDRH-Sponsored Obesity Weight-Loss Devices Study (CDRH-Obesity)

The Center for Devices and Radiological Health (CDRH) conducted a proof-of-principle study on the preferences of patients with obesity regarding the use of medical devices to achieve weight loss (MDIC PCBR website). This obesity study was a groundbreaking initiative by the U.S. Food and Drug Administration (FDA) to understand the preferences of patients who are candidates for emerging technologies and to use that information to inform regulatory assessment of those technologies. Information from the study was used in the January 2015 regulatory approval of the EnteroMedics Maestro Rechargeable System for weight loss.

At the time of the obesity study, there were a variety of weight-loss devices in the pipeline that would likely be pursuing FDA approval with a broad array of benefit-risk profiles, making benefit-risk comparison of these wide-ranging options challenging. Patients with obesity who are considering using a medical device to help them lose weight face difficult trade-offs because the more invasive options that offer the potential for greater weight loss also pose greater risks in terms of mortality and morbidity, and often require more restrictive dietary and exercise regimens than less invasive, but generally less-effective alternatives.

The FDA recognized the importance of considering the different benefit-risk profiles presented by different technologies rather than a "one-size-fits-all" approach. CDRH staff proposed a benefit-risk paradigm for designing clinical studies of obesity devices, which was formally presented to an FDA advisory panel for discussion in May 2012 and published as a proposal in a journal article in December 2012 (Lerner, 2012).

The choice to use a weight-loss device is "preference-sensitive" as some patients will accept the higher risks and more stringent diet and exercise requirements for a given amount of weight loss, whereas other patients will not. CDRH thought it would be useful to undertake a patient preference study to help frame the benefit-risk issues involved by quantifying the trade-offs patients are willing to make, including defining the minimum clinically meaningful benefit (weight loss) for a given risk profile.

The survey was conducted through a discrete choice experiment (DCE) whereby each respondent was asked to compare eight pairs of hypothetical devices defined by attributes, including benefits (amount and duration of weight loss), risks (mortality risk and risk of hospitalization), harms (duration of mild adverse events and type of operation), and other treatment attributes such as diet restrictions. Each attribute had three to five associated levels, selected with clinical expertise based on device profiles under review and anticipated to be submitted.

The results demonstrated that, based on preference score measurements, mortality risk was the most important attribute to patients, followed by weight loss, weight-loss duration, and side effect duration. Side effects that required hospitalization, type of surgery, and dietary restrictions were less important, although it was clear that patients did not like open surgery or having restrictions on sweets or hard-to-digest foods. Based on the preference scores, the authors calculated the minimum acceptable benefit (the minimum acceptable weight loss that patients expect from a device to tolerate a specific level of risk and other device attributes). They also calculated the maximum acceptable risk (the maximum device-related mortality risk that patients were willing to tolerate for a given level of weight loss and other device attributes). These results were used by CDRH to assist in the regulatory benefit-risk assessment process.

Section 9: References

SECTION 9

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