

# Value and Use of Patient- Reported Outcomes (PROs) in Assessing Effects of Medical Devices

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CDRH Strategic Priorities 2016-2017

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## **INTRODUCTION**

The Center for Devices and Radiological Health (CDRH or Center) is committed to our vision that patients have access to high-quality, safe, and effective medical devices and safe radiation-emitting products first in the world. We strive to ensure that patients and their care-partners stay at the center of our regulatory decision-making process. As part of our 2016-2017 Strategic Priorities<sup>1</sup>, we made a commitment to Partner with Patients to successfully achieve our mission and vision<sup>2</sup> in service of patients. One way we are partnering with patients is by incorporating the patient perspective as evidence in our decisions, including both patient preference information (PPI) and patient-reported outcomes (PROs).<sup>3</sup>

A PRO is, “A measurement based on a report that comes directly from the patient (i.e., study subject) about the status of a patient’s health condition without amendment or interpretation of the patient’s response by a clinician or anyone else.”<sup>4</sup>

Simply put, a PRO is a measurement of patients’ perception of their own health status or quality of life. Our interest is in those PROs that assess what is important to patients with the applicable disease or condition for which the PRO is being used.

A PRO instrument is a survey instrument scientifically designed, developed, and tested to accurately and reliably capture some concept(s) of self-perceived health status in a specific patient population. Some concepts can be observed (e.g., functionality and activity level) while others are unobservable and known only to the patients (e.g., pain intensity and anxiety level). Based on a patient’s response to these questions, a measurement can be computed to quantitatively assess the patient perspective of these concepts.

Common types of PRO measures include:

- Rating scales (e.g., numeric rating scale of pain intensity or verbal rating scale of global improvement of a medical treatment)
- Counts of events (e.g., patient-completed diary of seizure episodes)

PROs are commonly used in medical device regulatory submissions as a measure of the patient experience with a medical device. CDRH is actively working in this area to increase appropriate use and improve impact of PROs as evidence in regulatory decisions and beyond.

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<sup>1</sup> [2016 - 2017 CDRH Strategic Priorities](#)

<sup>2</sup> [CDRH Mission, Vision, and Shared Values](#)

<sup>3</sup> Since 2016, CDRH includes a summary of patient perspective data considered in PMA, HDE and de novo decisions. FDA decision summaries and other useful information are available in web-accessible searchable databases. For more information, see:

<https://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/default.htm>

<sup>4</sup> As defined in the BEST (Biomarkers, EndpointS, and other Tools) Resource Glossary, developed by FDA-NIH Biomarker Working Group. Available at: <https://www.ncbi.nlm.nih.gov/books/NBK326791/>

## **OBJECTIVES**

This report is intended to:

- 1) encourage the appropriate use of PROs in regulatory studies and decisions, and summarize our efforts and accomplishments to date,
- 2) inform medical device sponsors of case examples and other available resources to facilitate PRO data collection in pre- and postmarket clinical studies,
- 3) outline initial plans for addressing focus areas where the use of PROs is beneficial in regulatory submissions, and
- 4) identify areas of interest for potential future collaboration with stakeholders.

## **WHY FOCUS ON PROS**

### ***Value of PROs for Regulatory Decisions and More***

PRO measures can be used to capture a patient's everyday experience with a medical device, including experience outside of the clinician's office, and the effects of a treatment on a patient's activities of daily living. Furthermore, in some cases, PRO measures enable us to measure important health status information that cannot yet be detected by other measures, such as pain.

For clinical studies as well as clinical care, PRO measures are a standardized method of collecting a patient's health status directly from the patient, which can be useful for regulatory decisions as well as in clinical care. Clinical outcome assessments,<sup>5</sup> including PRO measures, can provide meaningful information that complements other clinical and physiological information or, in appropriate cases, be used in lieu of clinical and physiological endpoints. Together, clinical measures and PRO measures can provide a fuller picture of a patient's health, and the effects of a treatment on his/her symptoms, functioning, and quality of life.

A trial could be shaped to focus on outcomes that are important to patients and their care by using a patient-centric PRO measure as a study endpoint<sup>6</sup>. Moreover, utilizing PRO measures to assess effectiveness outcomes and/or collect adverse events due to a treatment could lead to fewer clinical visits within the trial as patients can report symptoms and events outside of the clinical setting.

For regulatory purposes, high quality information from PRO measures can provide valuable evidence for benefit-risk assessments,<sup>7</sup> and can be used in medical device labeling to communicate the effect of a treatment on patient symptoms, functioning and quality of life. PROs can be used to:

- 1) measure effectiveness for a device which may have a considerable effect on aspects which are of high importance to the patient or consumer, but may not be able to be adequately assessed by clinicians. For example: patients' perception of aesthetic devices; impact on symptoms of devices treating benign prostate hyperplasia.

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<sup>5</sup> [Clinical Outcome Assessment: BEST Glossary](#)

<sup>6</sup> [Basch, Ethan, et al. Overall Survival Results of a Trial Assessing Patient-Reported Outcomes for Symptom Monitoring During Routine Cancer Treatment. JAMA. 2017;318\(2\):197-198.](#)

<sup>7</sup> PROs, PPI, and other aspects of patient perspectives are included in IDE Benefit-Risk Assessments, as well as in Benefit-Risk Worksheets for PMAs, de Novo classifications and HDEs

- 2) measure effects of a device on the patient’s experience of the disease or condition outside the time window of a clinic visit. For example: functional ability with an orthopedic device.
- 3) measure effects of a device used in diseases or conditions which may have considerable effect on symptoms, functioning, quality of life, or other domains experienced by the patient. For example: heart failure symptom burden.
- 4) measure safety of a device by quantifying the number and severity of adverse events which affect symptoms, functioning, quality of life, or other domains experienced by the patient. For example: Measuring the frequency and severity of adverse events (e.g., nausea, vomiting, retching) for weight loss devices

Beyond regulatory uses, evidence from PRO measures may be useful for “downstream” decision-makers in the pathway to market, such as insurers and health care systems, for example as part of a value-based framework assessment<sup>8 9</sup>.

### ***Encouragement of PRO Usage***

In general, PRO measures have been increasingly used for regulatory purposes in CDRH over the last few years. Encouragement for the development of new PRO measures and increased utilization of existing PRO measures has stemmed from empowered patient groups, healthcare community, professional societies, and regulatory bodies.

#### *Encouragement by Patient Groups*

Some disease-specific communities have worked with the patient groups and regulators to develop recommendations on clinical study protocols and endpoints. For example, the Division of Cardiovascular Devices (DCD) worked with sponsors, academics, and the Centers for Medicare and Medicaid Services (CMS) through the Mitral Valve Academic Research Consortium to highlight the value of four patient-centered outcomes including symptoms, function, and quality of life one year following surgery<sup>10</sup>.

#### *Encouragement by Medicare Evidence Development & Coverage Advisory Committee*

On March 22, 2017, CMS convened a panel of the Medicare Evidence Development and Coverage Advisory Committee (MEDCAC) to examine what health outcomes in heart failure studies should be of interest to CMS, including quality of life measures (e.g., Kansas City Cardiomyopathy Questionnaire and Minnesota Living with Heart Failure Questionnaire)<sup>11</sup>.

Based on the panel vote, the members of the panel determined that certain quality of life measures: 1) are adequate measures which reflect the patient experience; and 2) should be included as composite standalone, meaningful primary health outcomes in research studies.

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<sup>8</sup> [Squitieri, Lee, et al. The Role of Patient-Reported Outcome Measures in Value-Based Payment Reform. \*Value in Health\*. 2017;20\(6\):834-836.](#)

<sup>9</sup> [Ayers, David. Implementation of Patient-reported Outcome Measures in Total Knee Arthroplasty. \*JAAOS\*. 2017;25:S48-S50.](#)

<sup>10</sup> [Stone, et al. Clinical trial design principles and endpoint definitions for transcatheter mitral valve repair and replacement: part 2: endpoint definitions: A consensus document from the Mitral Valve Academic Research Consortium. \*European Heart Journal\*. 2015; 36\(29\):1878-1891.](#)

<sup>11</sup> MEDCAC Meeting 3/22/2017 - Health Outcomes in Heart Failure Treatment Technology Studies. Information available at: <https://www.cms.gov/medicare-coverage-database/details/medcac-meeting-details.aspx?MEDCACId=73>

## ***Spike in PRO Data Collection in Regulatory Studies Reveals Challenges***

CDRH observed a >500% increase in the number of pre-market submissions that include PRO measures, over a 6-year period. These instruments range from general quality of life measures that provide an overview of a patient's total health status to disease and/or device-specific measures. This increase occurred prior to any focused initiative by CDRH, and therefore reflects increasing interest by study sponsors in obtaining PRO data.

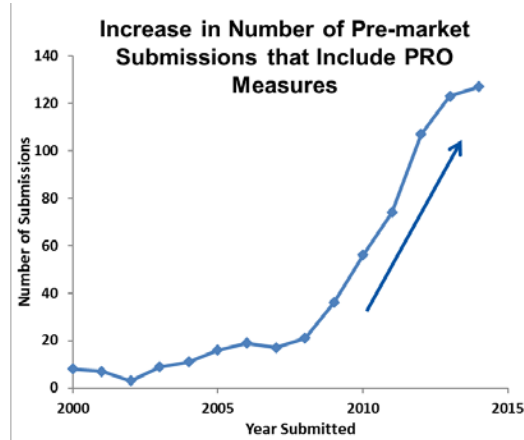


Figure 1: Number of submissions including PRO measures for calendar years 2000 – 2015.

In assessing this trend, CDRH identified several challenges:

1. Need for training on appropriate, predictable, and least-burdensome use of PROs
2. Need for increased transparency regarding use of PROs in regulatory decisions
3. Need for additional scientific expertise and capacity for submission review and early consultation and advice during study planning, and qualification of new PROs
4. Sponsor uncertainty in PRO review policies, such as level of validation required when PROs are used for different purposes

CDRH recognized a need and opportunity to work with sponsors to overcome these barriers to increased development, validation and qualification of PROs and appropriate use of patient-centered measures within clinical studies.

### ***Efficient Regulatory Adoption of PROs and other Tools—Medical Device Development Tool Program***

The Medical Device Development Tool (MDDT) Program was launched in 2017<sup>12</sup>, in part to assist sponsors with effectively incorporating PROs as well as other assessment tools into device clinical trials. The goal of the MDDT Program is to evaluate a tool within the selected context of use, and once qualified, allowing FDA review staff to accept the use of the tool without the need to reconfirm suitability and utility of the tool each time it is used. These device development tools include clinical outcome assessments (COA which include PRO measures), nonclinical assessment models (NAM), and biomarker tests (BT). The first PRO measure to be qualified under this program was the Kansas City

<sup>12</sup> [CDRH MDDT Program](#)

Cardiomyopathy Questionnaire (KCCQ) on October 19, 2017. We encourage the submission of more MDDT, including PRO measures, for potential qualification under this program.<sup>13</sup>

## **CDRH EFFORTS TO DATE & REGULATORY IMPACT**

### ***Increase Use and Transparency of Patient Input as Evidence in Our Decision-Making— A Strategic Priority Goal***

Our Partner with Patients strategic priority included two goals<sup>14</sup>. First, to Promote a Culture of Patient Engagement by Facilitating CDRH Interaction with patients. Second, to Increase Use and Transparency of Patient Input as Evidence in our Decision Making. In combining the art of patient engagement with the science of patient input, we are making good on our commitment to partner with patients in better achieving our mission and vision to improve the health and quality of life of patients.

One metric of success we adopted was to increase the number of appropriate patient perspective studies (e.g., those which evaluate patient reported outcomes or patient preferences) conducted and used in support of premarket and postmarket regulatory decisions.<sup>15</sup>

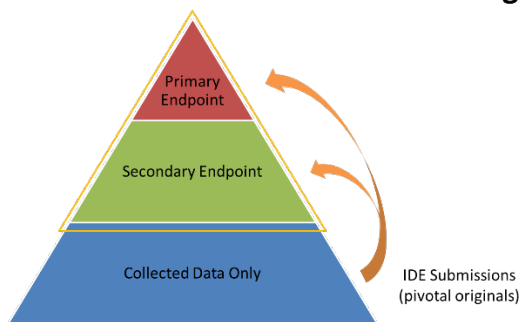
To support this goal, CDRH pledged to develop education and training for CDRH staff and industry on the development and use of the science of measuring and communicating patient input throughout the total product lifecycle, including PROs.

Additionally, CDRH committed to conduct a center-wide assessment of the state of PROs for pre- and postmarket regulatory uses, and to issue this report.

### ***Upgrading Appropriate PRO Use as Evidence in our Decisions***

We took steps to increase the use of PRO data to help inform regulatory decisions. For example, we have been encouraging inclusion of PROs in clinical studies, and voluntary upgrade of already collected PRO ancillary data to a secondary or primary study endpoint, where appropriate, as shown in figure 2.

#### **PRO involvement in decision-making**



*Figure 2. Upgrade of PROs involved in regulatory decision making.*

<sup>13</sup> [Scharen and Shuren. Medical Device Development Tools: Helping to Speed Medical Device Evaluation and Approval. FDA Voice 2017.](#)

<sup>14</sup> [2016 – 2017 CDRH Strategic Priorities](#)

<sup>15</sup> Compared to FY 2015 baseline.

## ***Focus on IDE and Early Stage Pre-Submission Interactions***

CDRH encourages inclusion of PROs in all pre-market submissions where appropriate<sup>16</sup>, with the caveat that the use of PROs in clinical studies is voluntary. For purposes of assessing effects of our strategic priority efforts, we focused on clinical studies subject to an investigational device exemption (IDE). These submissions contain clinical study protocols reviewed by the FDA.

The pre-submission stage is the recommended time frame to consider including a PRO within a clinical study design. These are often the earliest interactions between FDA and a study sponsor, and represent an opportune time to consider the value of including appropriate PROs as potential study endpoints in the clinical protocol. CDRH encourages sponsors to engage with us and discuss the use of PROs as endpoints, via a pre-submission<sup>17</sup>.

By engaging in early discussions with sponsors, CDRH aims to facilitate a patient-centric device evaluation approach while reducing the burden of late incorporation in trials. Early interactions between the sponsor and the review division can lead to cooperative decisions in determining the most appropriate PRO to include for the clinical endpoint of interest.

The downstream effect of this early interaction will potentially lead to least burdensome clinical studies through increased use of appropriate, high-quality PRO information as evidence in regulatory decisions such as PMA submissions, Post-Approval Studies and postmarket surveillance platforms that contain PROs. Such information may be valuable for post-regulatory decision-makers as well.

## ***METRICS & REGULATORY IMPACT***

### ***Continued Increase in Appropriate Premarket PRO Use Over FY16 & 17***

CDRH continued to see an increase in use of PRO measures over fiscal years 16 and 17, both in number and percentage of approved pivotal clinical trial IDEs that included a PRO measure within the study protocol. In FY17, over 75% of approved, pivotal original and new study IDEs submitted to the Office of Device Evaluation (ODE) included a PRO measure within the submission. PRO data was used in pre-market submissions submitted to all ODE Divisions. These results have been achieved by the mutual efforts of the Center and sponsors who increasingly recognize the value of including the patient perspective within clinical study protocols.

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<sup>16</sup> We recognize a PRO measure may not be relevant for certain types of devices or a particular aspect of disease under evaluation, for example, general surgical devices (e.g. scalpels) and some diagnostic tests.

<sup>17</sup> [The Pre-Submission Program and Meetings with Food and Drug Administration Staff](#)



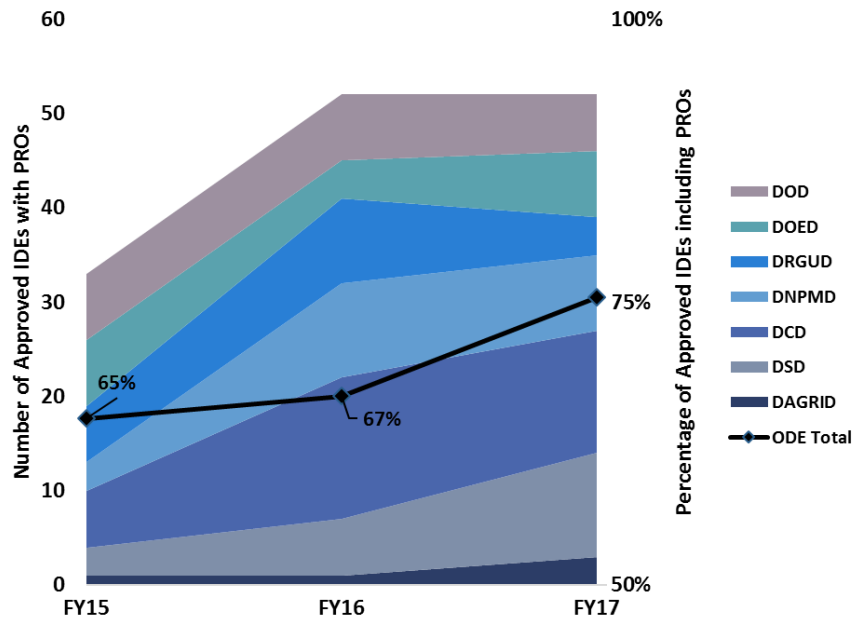


Figure 3 Final metrics of PROs in approved pivotal original and new study IDEs.

### ***PRO Use in Postmarket Mandated Studies***

As in premarket studies, in postmarket mandated studies, the patient perspective and experience is often, but not necessarily, complementary to clinical and other biological measures when evaluating the continued safety and effectiveness of an approved device.

Clinical post-approval studies (PAS) may be required at the time of approval of a Class III device, for continuing evaluation and periodic reporting on the safety, effectiveness and reliability of the device for its intended use<sup>18</sup>. These studies are a condition of approval and can be the continuation of the clinical study that supported the approval decision (i.e. extended follow-up of premarket cohorts) or a new enrollment clinical study<sup>19</sup>. FDA also has the authority to require postmarket surveillance studies under Section 522 of the FD&C Act.

Protocols for mandated clinical studies are developed with consultation between sponsors and FDA, to answer specific questions that may or may not benefit from the use of a PRO. For reaching our strategic priority goals, if a PRO would be helpful to address a postmarket question, we work with the sponsors to determine what instrument would be most appropriate, applying a least burdensome approach.

Assessing trends on the use of PROs in postmarket mandated studies is challenging because the number are driven by the questions that need to be addressed. To assess the use of PROs in postmarket mandated studies, we reviewed the new clinical studies ordered between FY 2015 to 2017 that had an approved protocol/study plan.<sup>20</sup> Table 1 below presents the number of PAS protocols that included a PRO.

<sup>18</sup> See 21 CFR 814.20(a)(2).

<sup>19</sup> Non-clinical studies can also be required as PAS, but are beyond the scope of this report.

<sup>20</sup> Clinical post-approval study (PAS) requirements involving the continued follow-up of premarket study cohorts were not included in this review as the pre-market study protocol is maintained, and already assessed in the premarket metrics section of this report.

Table 1 Distribution of New Mandated Clinical Studies with Approved Study Protocols/Plans using a PRO: for Orders Issued FY15-FY17, by Program and Fiscal Year

PAS Program			PS (522) Program		
Fiscal Year	Studies Including a PRO	%	Fiscal Year	Studies Including a PRO	%
2015	6/19	32	2015	0/1	0
2016	4/16	25	2016	2/2	100
2017	3/10	30	2017	0/0	-
Total	13/45	29	Total	2/3	67

### ***Facilitating PRO Collection Through Medical Device Registries***

CDRH has been working with medical device registry owners to increase data collection on the patient experience through incorporation of appropriate PROs. For example, the Function and Outcomes Research for Comparative Effectiveness in Total Joint Replacement (FORCE-TJR) Registry, Transcatheter Valve Therapy (TVT) Registry<sup>21</sup>, Comparing Options for Management: Patient-Centered Results for Uterine Fibroids (COMPARE-UF)<sup>22</sup>, and Pelvic Floor Disorder Registry (PFDR)<sup>23</sup> all contain PRO measures<sup>24</sup>. With the increased use of real-world evidence in regulatory review<sup>25</sup>, there is an opportunity to incorporate the patient experience through the PRO measures collected in registries and other real-world data sources.

### ***HIGHLIGHTED EXAMPLES OF PRO USE***

#### ***PROs Measuring Patient Priorities***

Use of PRO measures can facilitate the assessment of outcomes that are important to patients even if they are not paramount to a provider’s ability to provide clinical care. Examples include patients’ perception of aesthetic devices, impact on symptoms of devices to impact prostate health, and quality of life questionnaires in heart disease (see specific examples below).

Moreover, PRO measures can also capture patients’ health status and experiences outside of their clinical visits, such as frequency and severity of symptoms as well as everyday functioning. The impact of a treatment on a patient’s activities of daily life and quality of life can be instrumental information to help patients and healthcare providers when choosing the optimal treatment pathway<sup>26</sup>.

<sup>21</sup> [TVT Registry](#)

<sup>22</sup> [COMPARE-UF](#)

<sup>23</sup> [PFDR](#)

<sup>24</sup> [FORCE-TJR](#)

<sup>25</sup> [Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices](#)

<sup>26</sup> For additional information on PRO measures used to assessing patient priorities, see Appendix I

### ***PRO Use in Clinical Care***

The field of Orthopedics has a long history of PRO use in clinical care, which is reflected in the use of PRO data as evidence in regulatory decision making for orthopedic devices. From FY 2015 to 2017, 100% of pivotal original IDE pre-market orthopedic submissions included a patient-reported outcome measure. PRO instruments are used to measure safety and/or effectiveness of a novel device and to support labeling claims. They often serve as components of composite primary endpoints of clinical studies. Examples include PRO measures commonly used to quantify functional mobility, pain levels, and disability.<sup>27</sup>

### ***PROs as Safety Endpoints***

PROs can be used as a safety endpoint in a clinical study. It is important to measure adverse events and other negative outcomes to assess safety of new medical devices. A PRO can provide a standardized way to assess adverse events or differences in side effects between treatments. Examples include the measurement of pain through the visual analog scale (VAS) and the reporting of adverse events through diaries.

Other symptom-based PROs can also be used as measures of safety in clinical trials. For example, a PRO measure was used to capture the occurrence of abdominal pain, nausea, and vomiting by the Rhodes Index in the clinical trial for the ReShape IntraGastric Balloon.<sup>28</sup>

### ***Module Based PRO Measure***

Certain PRO platforms provide for a customizable measure specific to the treatment area and/or specific device. For example, the FACE-Q is a PRO measure designed to measure the satisfaction and quality of life for facial aesthetic procedures. The instrument was developed with multiple modules of quality of life scales, appearance scales, adverse event checklist, and patient experience of care scales. Modules can be chosen for a clinical study based on the specific treatment and/or general facial location where the device is used. For example, for a lip device, only modules relevant to the lip are utilized in the clinical study. Modules pertaining to other facial features (e.g., forehead) are removed for the specified clinical study. The customization limits the patient burden and assures all questionnaire items are relevant and appropriate for the patient cohort.<sup>29</sup>

### ***FUTURE OUTLOOK—CONTINUING TO INCORPORATE THE PATIENT VOICE***

As CDRH achieved our Partner with Patients commitments under our 2016-2017 Strategic Priorities, we will continue to encourage the appropriate use of patient perspective data within regulatory submissions. Table 2 below displays our approaches and solutions to support sponsors who wish to include the patient voice through PRO measures in clinical studies.

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<sup>27</sup> For additional information on the use of PRO measures for Orthopedic Devices, please refer to Appendix I

<sup>28</sup> For more information on using a PROM for device safety, and the ReShape clinical trial example, see appendix I.

<sup>29</sup> For additional information on the use of the FACE-Q questionnaire and other aesthetic PRO measures, please refer to Appendix I.

Table 2 Areas of focus and corresponding actions for incorporating PROs into clinical studies

Areas of Focus	Actions
Working towards a predictable and transparent review process	CDRH has committed to provide internal and external training on the evaluation of evidence that uses PRO data
Better understanding of how PROs can be appropriately incorporated into a clinical study	CDRH has developed a PRO compendium, supported with detailed case studies and examples on PRO usage to assist sponsors
Streamlining PRO development	CDRH has committed to perform “bridging studies” to adapt and update PRO measures for new indications and populations

***Resources to Facilitate Appropriate PRO Use in Pre- and Postmarket Studies***

The Center has developed resources and tools to assist sponsors who wish to include PRO measures in clinical studies.

***PRO Case Studies***

To clarify the potential application of PRO measures in clinical trials, **Appendix I** of this report includes detailed and self-contained examples of PROs used in approved pre-market approvals, de novos, humanitarian device exemptions, and 510(K) submissions. The PROs highlighted in these examples do not encompass all potential uses of PROs in device evaluation, but instead highlight various contexts in which PROs have been (e.g., effectiveness and safety endpoints) used in approved or cleared device submissions.

***PRO Compendium***

CDRH sees many examples of PRO measures used in clinical trials every year, but individual sponsors may not be aware of the utility of PROs in a particular device area. PRO data have been used to inform regulatory decisions across a wide variety of devices and indications at CDRH. To illustrate this, we developed a CDRH PRO Compendium in **Appendix II**. This Compendium lists some, but not all, of the PROs that can be used and reported in medical device pre-market clinical studies submitted to CDRH. We encourage sponsors interested in using a PRO in a clinical study to come talk with us through a pre-submissions meeting.

***MDUFA IV Outlook***

As part of the Medical Device User Fee Act IV (2018-2022), CDRH has committed to advance the science of patient input and its use in the regulatory process through the following:

- 1) **Build expertise and capacity.** Develop clinical, statistical, and other scientific expertise and staff capacity to respond to submissions containing applicant-proposed use of validated, voluntary patient preference information (PPI) or voluntary patient reported outcomes (PROs).
- 2) **Hold public meeting.** By the end of FY 2020, hold one or more public meetings to discuss PPI and PRO topics and publish the findings and next steps.
- 3) **Training, policy & research.** Undertake activities to improve the regulatory predictability and impact of PROs, including
  - a. Clarify to device review divisions that use of PROs is voluntary.
  - b. Outline in guidance a flexible framework for PRO validation with a “fit-for-purpose” discussion of evidence thresholds.
  - c. Work on developing a model for “bridging studies” to make efficient use of existing validated PROs.

Through these commitments we will continue to work with industry to include the patient perspective in regulatory submissions, where appropriate. We invite sponsors to discuss the incorporation of patient input into regulatory submissions through the pre-submission program.

### ***Build Expertise and Review Capacity in PRO Science***

CDRH strives to assure the review process is least burdensome, predictable, and transparent across the Center. To facilitate this for PROs, and We have and continue to develop education and training for lead reviewers, statisticians, and medical officers to build capacity within CDRH for reviewing PRO measures.

In the spring of 2017, staff across various Divisions were trained in the review of PROs, and how to encourage the appropriate usage of PROs while recognizing that inclusion of PRO measures is voluntary in most cases and sponsors may propose other approaches to measure key outcomes of interest. The 5 modules to the course included: (1) What is a PRO?, (2) Why are they important in regulatory decisions, (3) Development and validation, (4) Score interpretation, and (5) Evaluating the evidence supporting a PRO.

Additionally, the Center has invited external experts to speak at workshops on Item Response Theory, Patient Decision Aides, and an advanced psychometrics workshop discussing item-level evaluation, scoring algorithms, scale-level evaluation, and interpretation of scores and changes. These training efforts have laid a strong foundation for building scientific expertise and review capacity within CDRH.

The PRO review course developed in 2017 will be translated into an electronic interactive learning module. It will be required for new reviewers as part of the Reviewer Certification Program, and as a reference for existing staff. We will continue to provide training within the Center for reviewers on PRO measure development, evaluation, and use.

### ***Fit-for-purpose Evidence Thresholds for PRO Validation***

CDRH recognizes that there is a spectrum of PRO uses within a clinical study. This can include measures of safety or effectiveness, use as primary or secondary endpoints, use as a stand-alone measure or component of a composite endpoint. Appropriate thresholds for validation evidence should be based on the context of use of the PRO. The level of validation required for a PRO measure depends on its proposed usage in a clinical study. CDRH will develop a “fit-for-purpose” framework for assessing validation evidence, and seek public input. The goal is to improve predictability by clarifying the methodology used to review PROs for various types of uses in premarket and postmarket review.

### ***Bridging Studies for Efficient Adaptation of Existing PROs***

Bridging studies provide an opportunity to reduce the burden of using PROs in regulatory studies by building on existing PRO measures. For new device technologies, PRO measures can be used to assess the device’s novel functions, outcomes, adverse events, etc. In some cases, a bridging study can be used to adapt and/or modify an existing PRO measure for a new context of use, rather than creating a new instrument. Some examples of bridging studies are:

*Paper to Electronic:* The instrument is currently given on pen and paper but would be easier for patients to complete if given via electronic format. Electronic data capture may also streamline data

collection by eliminating or reducing manual data entry by a site or data coordinating center, which increases data quality and reduces site burden.

*Population Adaptation:* A measure is used for a specific and/or general population that could be adapted and/or specified for a different population of users. Examples include, but are not limited to, adapting a pediatric PRO measure from an adult instrument, adapting a measure used for more severe stages of disease to be used in less severe patients, and updating a sex-neutral PRO measure to be appropriate for sex-specific symptoms/needs.

*Novel Technology Adaptation:* Revision of a current measure to address developments for a novel technology where no PRO currently exists to measure health status.

*Broadening Perspective:* The addition of items to an instrument so that the PRO measure more thoroughly captures the patient's experience or response to treatment.

*Reduction of Items:* A reduction in the number of questions in an instrument may be desirable to reduce patient burden and ensure the relevance of PRO data to the evaluation of a medical device.

*Terminology Update:* The modernization of terminology and/or items may be needed for an outdated measure when there have been changes in the disease area or device capabilities.

As part of our commitments with MDUFA IV, CDRH will develop a template for sponsors who choose to perform a bridging study to develop or modify a PRO measure to facilitate their conduct and reporting of the study.

## **CONCLUSION**

PROs play an important role in assessing the patient experience with a medical device, and can provide valuable evidence for regulatory decisions, payers, and health system customers. PROs are commonly used in medical device regulatory submissions. CDRH is working collaboratively with our customers to increase appropriate use and increase the value of PROs as evidence in regulatory decisions and for other, non-FDA purposes. Our efforts to date, including staff training, assessment of various PRO uses across CDRH, and development of resources for industry and staff, have reduced barriers to appropriate use and improved the regulatory impact of PROs. We are committed to continuing to advance the science of patient input and its use in the regulatory process throughout MDUFA IV and thereafter. We invite sponsors, patients, PRO experts, and other customers to collaborate with us as we continue to incorporate the patient voice in our daily work.

**NOTE: The purpose of the Appendix is to provide context and details about selected successful cases of using PROs to the audience to facilitate uptake. The cases will be hyperlinked to the corresponding part of the main text in the PRO Report and the compendium list.**

## PRO Report

### Appendix: Patient-Reported Outcome Measure (PRO) Case Studies

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## **Growing Acceptance: PROs for Cardiovascular Devices**

### *Regulatory Context*

In chronic conditions such as heart failure (HF), patient-reported outcome measures (PROs) can play an important role in quantifying the impact on a patient's health status, in addition to the traditional clinical endpoints of hospitalizations and mortality. Deficiencies in heart function coincide with a significant detriment to various aspects of a patient's quality of life and everyday function. PROs have and continue to play an important role in HF-related submissions in the Division of Cardiovascular Devices (DCD) because of the nature of the syndrome. The treatment of HF not only focuses on preventing disease progression, but also aims to ameliorate symptoms and improve the patient's quality of life.

To evaluate full patient experience, clinical trials not only collect hard outcomes, such as hospitalizations and mortality, and biological measures, such as ejection fraction or various biomarkers, but also evaluate the patient's experience, including symptomatology and physical limitations, aspects often best measured using PROs. Clinical outcome assessments, such as PROs, can be evaluated in such a way that is useful in a regulatory setting. Therefore, well-studied measures of the impact of HF on quality of life and daily function have allowed sponsors to include PROs as important endpoints in clinical studies and pre-market applications submitted to DCD.

### *Example Patient-Reported Outcome*

For example, the Kansas City Cardiomyopathy Questionnaire (KCCQ) was developed to provide a measure of disease specific health-status in patients with heart failure. Several aspects of the KCCQ have warranted its inclusion in relevant trials. Systematic reviews evaluating PROs in heart failure found good measurement properties.<sup>1,2</sup> Additionally, numerous studies of heart failure have either evaluated or utilized the PRO. The KCCQ has also been evaluated and used with other forms of heart disease, including aortic stenosis.<sup>3,4</sup> The KCCQ includes questions covering physical limitations, different aspects of symptoms, quality of life, social interference, and self-efficacy, with two available summary scores, a functional status score and a clinical summary score.<sup>5</sup> The KCCQ was designed to include the most important aspects of a patient's experience related to his/her HF and quantify them. It has been evaluated for the ability to detect clinical change.<sup>5,6</sup> The KCCQ's performance in patients with HF with preserved and reduced ejection fraction has also been evaluated<sup>7</sup>, as well as its relationship to risk of HF related hospitalization or death.<sup>8</sup> Overall, there are a number of studies evaluating the different aspects of the KCCQ, providing the opportunity to compare its statistical and psychometric properties to the needs of a particular trial. A thorough review of the properties of the KCCQ was undertaken as part of the Medical Device Development tool program (MDDT), resulting in the KCCQ's qualification as the first MDDT tool.<sup>9</sup> Qualification of the KCCQ means that FDA staff can rely on the measure without having to reconfirm that the tool is suitable for use in the qualified context of use. This means time and money is saved preparing for and conducting the review of a PRO within a prospective clinical trial. Beyond the particulars of the statistical and psychometric properties of the KCCQ, the fact that it can systematically capture a patient's evaluation of how his/her HF affects his/her life can be beneficial for evaluating the impact of a device or treatment with a focus on the patient.



### *Patient-Reported Outcome Use*

The KCCQ is one PRO that has been widely collected in clinical trials supporting regulatory decision making at the center for not only devices to treat HF, but devices for other forms of heart disease as well. In a recent approval through Pre-Market Approval (PMA) for a device indicated for a form of heart disease, [P140031](#),<sup>10</sup> the KCCQ was used as ancillary data. At the initial decision date, the results utilizing the KCCQ were referenced in the effectiveness conclusions of the summary of safety and effectiveness data, and in the booklet for patients. A few other PMA approvals, both for heart failure and other heart disease, informed by KCCQ include: [P130009](#),<sup>11</sup> [P100009](#),<sup>12</sup> and [P100047](#).<sup>13</sup> Additionally, a recent search of [clinicaltrials.gov](http://clinicaltrials.gov) resulted in 105 results for the term “KCCQ”, suggesting it has been commonly used in clinical trials.

### *Impact and Summary*

As the evidence and experience with the PROs like KCCQ accumulate in clinical practices and clinical trials, their role as a key piece of evidence to inform pre-market application approvals will continue to grow. Moreover, the impact of a patient’s treatment on multiple facets of his/her life has been widely recognized by the public. The development and continued evaluation of PROs to measure this experience will be necessary to ensure the PRO is sufficiently supported for use in decision making.

## **Adaptive by Design: PROs for Aesthetic Devices**

### *Regulatory Context*

A goal of aesthetic and reconstructive procedures or plastic surgery is patient satisfaction with the results. In the absence of objective measures, the success of a treatment utilizing an aesthetic device can be difficult to define and even more difficult to measure. Therefore, scientific assessments from the clinician's or patient's perspective are essential for device evaluations. The clinician's expertise is necessary to evaluate certain aspects of success and help evaluate clinical effectiveness. Thus, clinician evaluation will remain an integral part of evaluating aesthetic devices. However, how the patient feels about the results of the procedure are also important, but often overlooked. Information directly from the patient will be necessary to fully capture the effectiveness of the procedure, such as satisfaction or the impact on quality of life.

### *Example Patient-Reported Outcomes and Use*

A common scale used to assess improvement in aesthetic procedures is the Global Aesthetic Improvement Scale (GAIS), which is often filled out by the clinician or investigator, as seen in 510(k) submission [K161885](#).<sup>14</sup> However, the scale has limits as clinical evidence to inform regulatory decision making. First, it lacks standardization, as can be seen in the variation in response options and descriptions from study to study.<sup>e.g.15,16</sup> Second, despite widespread use, the GAIS has a lack of methodological or developmental evidence supporting the reliability and validity of scores obtained from its use. These deficiencies limit the use of the scores obtained from the measure in regulatory decision making.

There are other PROs used in aesthetic device trials to help evaluate effectiveness. The choice of PRO is dependent on the indication for use and the anatomical location of use for the device. Some PROs, targeted to different aspects of aesthetic surgery, have been developed, evaluated, and used as evidence in clinical trials. For example, the Breast Evaluation Questionnaire (BEQ) was used as a piece of the effectiveness evaluation for the saline-filled breast implant in Pre-Market Approval submission [P120011](#).<sup>17</sup> The BEQ was developed for use with patients undergoing breast implant surgery to assess their satisfaction with their breasts before and after surgery.<sup>18</sup>

### *Future Directions*

The use of targeted PROs, specific to the indication or area under treatment, leads to the need for class of modular PROs that can be adapted for a wide variety of indications and locations of treatment such as the FACE-Q<sup>®19</sup> and BREAST-Q<sup>®20</sup>. The FACE-Q<sup>®</sup> is composed of over 40 separate modules, each designed for use and scoring independently. In any given study, only a subset of the scales needs to be administered. The scales of the FACE-Q<sup>®</sup>, for example, are broken into four domains: appearance appraisal scales, adverse effect checklist, process of cares scales, and quality of life scales. The domains are further sub-divided; with the appearance appraisal scales including scales evaluating forehead lines, eyelashes, cheekbones, nasolabial folds, among others. The variety of scales, targeted to specific facial features, provide flexibility to choose the PRO best suited to measure the endpoint of interest. Importantly, there is published evidence of the development and psychometric properties of the scales included in the FACE-Q<sup>®</sup> and BREAST-Q<sup>®</sup>, including the ongoing effort to accumulate evidence of the validity of the scores when the scales are used in various situations.

### *Impact and Summary*

The difficulty in judging the effectiveness of aesthetic and reconstructive procedures is partly due to the impact of perceptions and emotions this evaluation. Despite the difficulty in assessing the success of aesthetic procedures, scientific approaches can be used to capture the patient's perspective in a useful format, such as the development of PROs. The use of a PRO in a regulatory capacity naturally necessitates evidence supporting that use. As the evidence supporting a particular use of a PRO accumulates, the utility of the PRO in a regulatory environment increases. The development and approval of aesthetic devices will only benefit from the continued development and evaluation of PROs.

## Essential Components of Primary Endpoints: PROs for Orthopedic Devices

### *Regulatory Context*

Patients who use orthopedic devices have commonly sought treatment to alleviate pain and increase or restore function.<sup>21,22</sup> In the Division of Orthopedic Devices (DOD), many of the pivotal studies supporting pre-market applications used composite endpoints, a combination of clinically relevant endpoints. For example, a patient's treatment success can consist of criteria including pain, function, and radiographs. The composite endpoints of these studies tended to include pain and functional ability because of their importance to patients and their importance as indicators of effectiveness. This has led to the widespread inclusion of patient-reported outcome measures (PROs) in pre-market submissions in the DOD, as pain is only effectively measured through patient report and patient-reported functional ability encompasses a wider range of activities than can be measured clinically or through performance measures.

The widespread use of PROs in DOD applications is due in part to the availability of well-researched measures specific to locations or conditions related to the device application. The common PROs in submissions to DOD can generally be classified into two broad areas: measures of pain and measures of function. The measures of function are primarily used to evaluate effectiveness, while pain serves as both safety and effectiveness endpoints. Certainly this is very general, and not all PROs fit this framework, however it is a helpful schema for discussing the use of PROs in DOD submissions. While there are numerous examples of the use of PROs in DOD submissions, focus here is given to submissions referenced in the compendium.

### *Patient-Reported Outcome Use*

The use of PROs to evaluate functional ability and similar concepts provides multiple benefits when used in conjunction with other measures, such as imaging or performance assessments. Patient reported function can provide a broader view of function than can be assessed in a clinical setting. For instance, physical function, including activities of daily living, may be best assessed from the patient's perspective, without the need for interpretation by a trained professional. Additionally, physical function can play an important role in many phases of a trial. In the DOD, loss of function can be among the indicators for inclusion in a trial. Functional status, as measured by the Neck Disability Index (NDI),<sup>23</sup> was used as a part of the inclusion criteria for the trial supporting the submission [P140019](#).<sup>24</sup> Similarly, the physical function scale of the Zurich Claudication Questionnaire (ZCQ),<sup>25</sup> a disease-specific measure for patients with lumbar spinal stenosis, was used in [P140004](#)<sup>26</sup> as one of the clinical components used to define moderate degenerative lumbar spinal stenosis, part of the inclusion criteria for the trial. How the patient is affected by the disease or condition plays an important role in determining the need and course of treatment and that information is often best captured directly from the patient through a standardized set of questions.

Beyond inclusion criteria, function is also used as part of composite and co-primary endpoints, supporting the safety and efficacy of a submission. In [P120024](#),<sup>27</sup> the Oswestry Disability Index (ODI),<sup>28,29</sup> a condition-specific outcome measure for lumbar spinal disorders,<sup>29</sup> was used in a composite endpoint for determination of overall success, along with maintenance or improvement in neurological status, maintenance or improvement in range of motion at the operative level based on radiographs, absence

of subsequent surgical interventions at the operative level, and no serious device-related adverse events. Success on the ODI was defined as at least a 15 point improvement from baseline at 24 months. In [P140019](#),<sup>24</sup> the NDI was used as a component of the efficacy endpoint along with fusion status and neurological success at 12 months, in a non-inferiority study. In another submission, [P140004](#),<sup>26</sup> clinical efficacy was defined as improvement on two of the three domains within the ZCQ. The primary composite success measurement included clinically significant improvement in ZCQ scores, absence of subsequent surgical interventions at the operatively treated level(s), absence of implant or procedural-related complications, and no clinically significant confounding treatments such as injections or nerve block procedures. As seen in the previous examples, measures of physical function play a role in evaluating the overall safety and effectiveness of a device. A well developed and relevant PRO can help complete the picture, and provide sound information from the patient's perspective.

In addition to function, the evaluation of pain often plays a crucial role in the evaluation of a submission. Some devices are used to treat the underlying condition that may be causing pain, alleviating or ameliorating said pain, while others evaluate the presence of pain due to implantation of the device. [P100006](#)<sup>30</sup> provides an example where self-reported measures of pain, along with self- and clinician-reported measures of physical function, played a crucial role in establishing effectiveness. The summary of safety and effectiveness data stated that consensus could not be reached regarding the interpretation of the radiological finding. Consequently, a post-hoc analysis of pain at fusion site, the Foot Function Index (FFI),<sup>31,32</sup> and the American Orthopedic Foot and Ankle Score (AOFAS) was undertaken to demonstrate non-inferiority to the control. The FFI is a PRO developed to measure the impact of foot pathology on function, and the AOFAS is a clinician rated measure of ankle and hindfoot function. Pain was measured using the visual analog scale. In another example, pain was the primary efficacy endpoint for [P150010](#),<sup>33</sup> measured using the Western Ontario and McMaster Universities Osteoarthritis Index part A (WOMAC A),<sup>34</sup> which is comprised of a visual analog scale. In the trial, the results of the comparison of the treatment and control pain reduction score at 180 days were non-significant. Consequently, a non-inferiority comparison to a previously approved submission was undertaken, taking advantage of the previous study's use of the visual analog scale to measure pain. The use of a comparable measure of self-reported pain allowed for the comparison of the two studies. The ability to compare across studies lends support to the use of comparable measures across studies, when those measures are well established and the scores are well validated for the intended purpose.

### *Impact and Summary*

As shown, patient-reported outcome measures, when properly included, can support the totality of evidence needed for a submission. The availability of condition or location specific measures of function, along with measures of pain provides the opportunity to include patient perspectives on treatment safety and effectiveness in a useful manner in submission to the DOD. However, selecting the right PRO, and evaluating the support for its validity for a particular use is essential.

## **Critical Evidence as Primary and Secondary Endpoints: PROs for Devices Treating Benign Prostate Hyperplasia**

### *Regulatory Context*

According to the guidance to industry, in studies to evaluate devices for the treatment of benign prostate hyperplasia (BPH), “the primary effectiveness endpoint should be one that is clinically meaningful and, ideally, should fully characterize the effect of treatment.”<sup>35</sup> The symptoms that cause patients to seek diagnosis and treatment, such as frequent and urgent need to urinate, weak urine stream, incomplete emptying, and nocturia are subjective and collectively known as lower urinary tract symptoms (LUTS). Generally, treatment of LUTS secondary to BPH has focused on the alleviation of symptoms, and the prevention of disease progression.<sup>36</sup> Consequently, measures of these symptoms and their impact on the patient have become a necessary component to evaluate treatment impact. In addition, sexual dysfunction has been a known side effect of BPH<sup>35</sup> and some of its treatments.<sup>37</sup> Effective measures of male sexual functioning are also, by nature, self-reported.

### *Example Patient-Reported Outcomes*

To best measure the severity and impact of LUTS as well as the side effects of treatment on a patient’s life, that information needs to come directly from the patient. Standardizing the assessment of the severity and impact of LUTS as a patient-reported outcome measure (PRO) would then yield more reliable, precise, and robust information for regulatory decision making. The development of such a measure resulted initially in the American Urological Association Symptom Index,<sup>38</sup> which was later adapted and renamed the International Prostate Symptom Score (I-PSS). Since then the I-PSS has become an integral part of treatment assessment for LUTS secondary to BPH. At the same time, measures of male sexual function are used to evaluate the safety of the procedure.

The I-PSS is a well-established measure. It is supported by the American Urological Association and is recommended for use in investigations of devices used to treat BPH.<sup>35</sup> There is a body of published literature<sup>39-43</sup> supporting the validity of the I-PSS, including comparisons to urodynamic testing. A definition of the change in score that might constitute a clinically meaningful improvement has also been established and utilized.<sup>42</sup> Another PRO, the International Index of Erectile Function (IIEF), is also well-supported in the literature, recommended by the 1<sup>st</sup> International Consultation on Erectile Dysfunction, and used in previous clinical trials.<sup>44</sup> There is also evidence of a clinically meaningful difference for specific domains of the scale.<sup>45</sup> The evidence supporting the validity of both measures has led to confidence in the use of both PROs in the pivotal studies. The medical community considers the content assessed by the PROs to be relevant to LUTS secondary to BPH and the patient’s experience. Moreover, the psychometric properties of these PROs have been evaluated and demonstrated in clinical studies and patient populations similar to those under evaluation in submissions, demonstrating properties important to their specific use such as reliability and sensitivity to change.

### *Patient-Reported Outcome Use*

The utility of both the I-PSS and IIEF are demonstrated in the De Novo re-classification of a device to treat symptoms due to urinary outflow obstruction secondary to BPH. For example, both the I-PSS and the IIEF played a critical role to inform our decision to grant the De Novo<sup>46</sup> ([DEN130023](#)). The I-PSS was used as the primary endpoint in a superiority clinical trial design, evaluating the change in I-PSS scores at 3 and 6 months compared to baseline. The IIEF was used to monitor change in sexual function at 12

months. The change in I-PSS endpoint was met in the study, while there was no statistically significant change in IIEF. In addition, all other secondary clinical parameters were significantly improved, supporting the conclusions drawn from improvement in the I-PSS.

### *Impact and Summary*

The impact of treating LUTS secondary to BPH is primarily known to the patient alone. Patient reported outcomes are necessary to evaluate any improvement in symptoms, and to assess the loss or preservation of sexual function. Both the I-PSS and the IIEF benefited from a development goal of evaluating treatment efficacy.<sup>38,47</sup> In the years since their development, a variety of research supporting the various aspects of the validity of their scores for making determinations in clinical trials has accumulated. Consequently, the existence of well-established and researched PROs has benefited the ability to make regulatory decisions directly related to patient impact. The development and continued research on PROs benefits the Center's ability to include patient's perspectives in meaningful ways.

## Patient Experience as safety measures: PROs for Weight Loss Devices

### *Regulatory Context*

The guidance for industry and FDA staff on benefit/risk assessment in premarket approval and De Novo classification notes the use of patient reported outcome measures to demonstrate benefit in the product approval process.<sup>48</sup> PROs can help quantify the impact of a device or treatment on a patient's well-being and allow sponsors to capture factors that are important to patients. The use of PROs is not limited to the evaluation of benefit and effectiveness. There are aspects of safety/risk that are best determined by the collection of patient input utilizing PROs.

The important aspects of probable risks include the severity, type, number, and rates of the events associated with the use of the device, as well as the probability and duration of the events.<sup>48</sup> Many of the events are tracked as either present or not. For others, such as many serious events, the level of severity is important and diagnostic testing or expert evaluation is necessary to identify and treat. Of course, any type of adverse event (AE) may require report by the patient. At the same time, while adverse events such as pain, nausea, and vomiting can either be present or not, and have different levels of severity, their presence and severity is best evaluated through patient report. Events such as pain and nausea are internal to the patient and lack objective, external diagnosis criteria. Consequently, a standardized, easily interpreted report through the use of a patient reported outcome measure is useful in evaluating the presence and severity of such events. Plus, there is evidence that compared to patient-report, clinician-report often underestimates the occurrence of AEs.<sup>49</sup> Other evidence shows that clinician-reported AEs may only be moderately reliable,<sup>50</sup> further necessitating the collection of patient-reported AEs.

### *Patient-Reported Outcome Use*

The REDUCE clinical trial for the ReShape intragastric balloon,<sup>51</sup> summarized in [P140012](#), is an example suggestive of potential uses of PROs in assessing safety in a device submission. The ReShape system is indicated for weight reduction when used in conjunction with diet and exercise, in obese patients with a body mass index of 30-40 kg/m<sup>2</sup> and one or more obesity-related comorbid conditions. The assessment of safety for the device included a full review of adverse events and serious adverse events, changes in vital signs and laboratory values, as well as symptoms of abdominal pain, nausea, and vomiting. The symptoms of abdominal pain, nausea, and vomiting were assessed using two PROs, an abdominal pain visual analogue scale (VAS) and the Rhodes Index for Nausea, Vomiting, and Retching.<sup>52</sup>

The VAS, in this case used for abdominal pain, is a generally common measure used to assess pain, and can be modified to refer to a variety pain locations, types, or time frames. The VAS consists of a single horizontal or vertical line, usually 100mm in length, with anchors of 'no pain' and 'extreme pain' or the like at the ends. The patient is asked to mark their level of pain relative to the line and anchors. The VAS is cited for its simplicity.<sup>53</sup> Reviews of pain measures have found evidence supporting its reliability and sensitivity to changes in pain.<sup>54-56</sup> There are some concerns regarding the accuracy of reports when using the VAS in elderly populations,<sup>57,58</sup> and measurement error may be introduced through changes in line length due to printing or photocopying.<sup>53</sup> However, the concern with elderly patients was not relevant to the REDUCE clinical trial.

The assessment of nausea, vomiting, and retching (NVR) is usually best obtained through self-report questionnaires providing the patient's perspective.<sup>59</sup> The Rhodes Index was originally developed for use



in cancer patients undergoing chemotherapy.<sup>60</sup> The original scale has seen wide use in oncology, obstetrics, and surgery research.<sup>52</sup> There is other obesity research utilizing the Rhodes Index,<sup>61</sup> however, the questionnaire was not used in other trials for endoscopic devices for obesity around the same time.

### *Impact and Summary*

Symptoms of nausea and vomiting are expected with the use of devices such as the ReShape intragastric balloon and had been seen in previous intragastric balloons.<sup>62,63</sup> They may be temporary in nature after placement of the device while the patient adjusts to the balloon, however, they can persist and lead to the removal of the device.<sup>63</sup> In the REDUCE trial for the ReShape device, the Rhodes index showed that despite the presence of these symptoms the severity declined over time, with the summary of safety and effectiveness data noting they usually resolve in 30 days. This showed that the symptoms of nausea and vomiting, while due to implantation, are likely to resolve while the device is still present.

Some aspects of treatment, whether effectiveness or safety, are best or can only be measured by patient report. In terms of adverse events, a well-supported patient-reported outcome measure allows not only tracking the presence of the event, but also an estimate of the severity and impact on the patient's life. As in the REDUCE trial, the combination of PRO data with tracking of other events can provide a complete picture of the safety and tolerability of a device. Thus, the inclusion of PROs can further elucidate and track important outcomes in establishing safety.

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## The Center for Devices and Radiological Health Patient-Reported Outcomes Compendium

The CDRH PRO Compendium is not a comprehensive list of PROs and is not intended to replace either existing disease-specific guidance or key interactions with FDA concerning device development. **Please note, the compendium only includes selected PROs appearing in device labels based on recent approvals and classifications.**

Device sponsors are strongly encouraged to seek advice from the relevant division early in the development process to discuss the selection and implementation of PROs specific to their program, irrespective of whether the PRO is included in the Compendium.

Some of the PROs listed in the compendium may be protected by proprietary rights, and in some cases, a royalty and fee may be charged by the copyright owners for their authorized use. The inclusion of a PRO in the compendium does not equate to an endorsement by FDA.

[Patient-Reported Outcome Compendium](#)

The CDRH PRO Compendium includes the following columns:

Columns	Elements	Description of Content
Column 1	Fiscal Year	Fiscal year of final approval or classification
Column 2	Submission Number	Number associated with the specific submission
Column 3	Date of Final Decision	Date of final approval or classification
Column 4	Center/Office/Division/Branch	The Center, Office, Division, and Branch that reviewed the submission
Column 5	Applicant	Name of applicant for the submission
Column 6	Product Code	Identifies the generic category of the device, based upon the medical device product classification designated under 21 CFR Parts 862-892
Column 7	Generic Name	Generic device name as stated in the public summary
Column 8	Trade Name	Device trade name as stated in the public summary
Column 9	Patient-Reported Outcome Measure	Name of the Patient-Reported Outcome measure utilized in the submission
Column 10	PROM Abbreviation	Common abbreviation of the PROM
Column 11	PROM Description	A general description of the PROM
Column 12	PROM Usage	Endpoint for the PROM identified in the public summary
Column 13	Device Indication for Use	The device indication for use take from the public summary
Column 14	Appears in Labeling	Whether or not the PRO appears in labeling materials included in the public summary
Column 15	Selected Reference	AMA citation for the development publication, user manual or other relevant publication for the PRO
Column 16	PubMed ID for Publication	The PubMed ID number and link for the selected reference, where available
Column 17	Additional Reference	Additional AMA citation for the development publication, user manual or other relevant publication for the PRO
Column 18	PubMed ID	The PubMed ID number and link for the additional reference, where available
Column 19	Notes	Any notes needed to aid in interpretation of the file.