

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.^{1,2} 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.^{3,4} 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.⁵ 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.^{5,6} The KCCQ's performance in patients with HF with preserved and reduced ejection fraction has also been evaluated⁷, as well as its relationship to risk of HF related hospitalization or death.⁸ 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.⁹ 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](#),¹⁰ 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](#),¹¹ [P100009](#),¹² and [P100047](#).¹³ Additionally, a recent search of 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](#).¹⁴ 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.^{e.g.15,16} 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](#).¹⁷ The BEQ was developed for use with patients undergoing breast implant surgery to assess their satisfaction with their breasts before and after surgery.¹⁸

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^{®19} and BREAST-Q^{®20}. The FACE-Q[®] 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[®], 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[®] and BREAST-Q[®], 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.^{21,22} 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),²³ was used as a part of the inclusion criteria for the trial supporting the submission [P140019](#).²⁴ Similarly, the physical function scale of the Zurich Claudication Questionnaire (ZCQ),²⁵ a disease-specific measure for patients with lumbar spinal stenosis, was used in [P140004](#)²⁶ 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](#),²⁷ the Oswestry Disability Index (ODI),^{28,29} a condition-specific outcome measure for lumbar spinal disorders,²⁹ 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](#),²⁴ 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](#),²⁶ 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](#)³⁰ 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),^{31,32} 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](#),³³ measured using the Western Ontario and McMaster Universities Osteoarthritis Index part A (WOMAC A),³⁴ 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.”³⁵ 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.³⁶ 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 BPH³⁵ and some of its treatments.³⁷ 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,³⁸ 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.³⁵ There is a body of published literature³⁹⁻⁴³ 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.⁴² Another PRO, the International Index of Erectile Function (IIEF), is also well-supported in the literature, recommended by the 1st International Consultation on Erectile Dysfunction, and used in previous clinical trials.⁴⁴ There is also evidence of a clinically meaningful difference for specific domains of the scale.⁴⁵ 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 Novo⁴⁶ ([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.^{38,47} 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.⁴⁸ 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.⁴⁸ 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.⁴⁹ Other evidence shows that clinician-reported AEs may only be moderately reliable,⁵⁰ further necessitating the collection of patient-reported AEs.

Patient-Reported Outcome Use

The REDUCE clinical trial for the ReShape intragastric balloon,⁵¹ 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/m² 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.⁵²

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.⁵³ Reviews of pain measures have found evidence supporting its reliability and sensitivity to changes in pain.⁵⁴⁻⁵⁶ There are some concerns regarding the accuracy of reports when using the VAS in elderly populations,^{57,58} and measurement error may be introduced through changes in line length due to printing or photocopying.⁵³ 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.⁵⁹ The Rhodes Index was originally developed for use

in cancer patients undergoing chemotherapy.⁶⁰ The original scale has seen wide use in oncology, obstetrics, and surgery research.⁵² There is other obesity research utilizing the Rhodes Index,⁶¹ 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.^{62,63} 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.⁶³ 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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