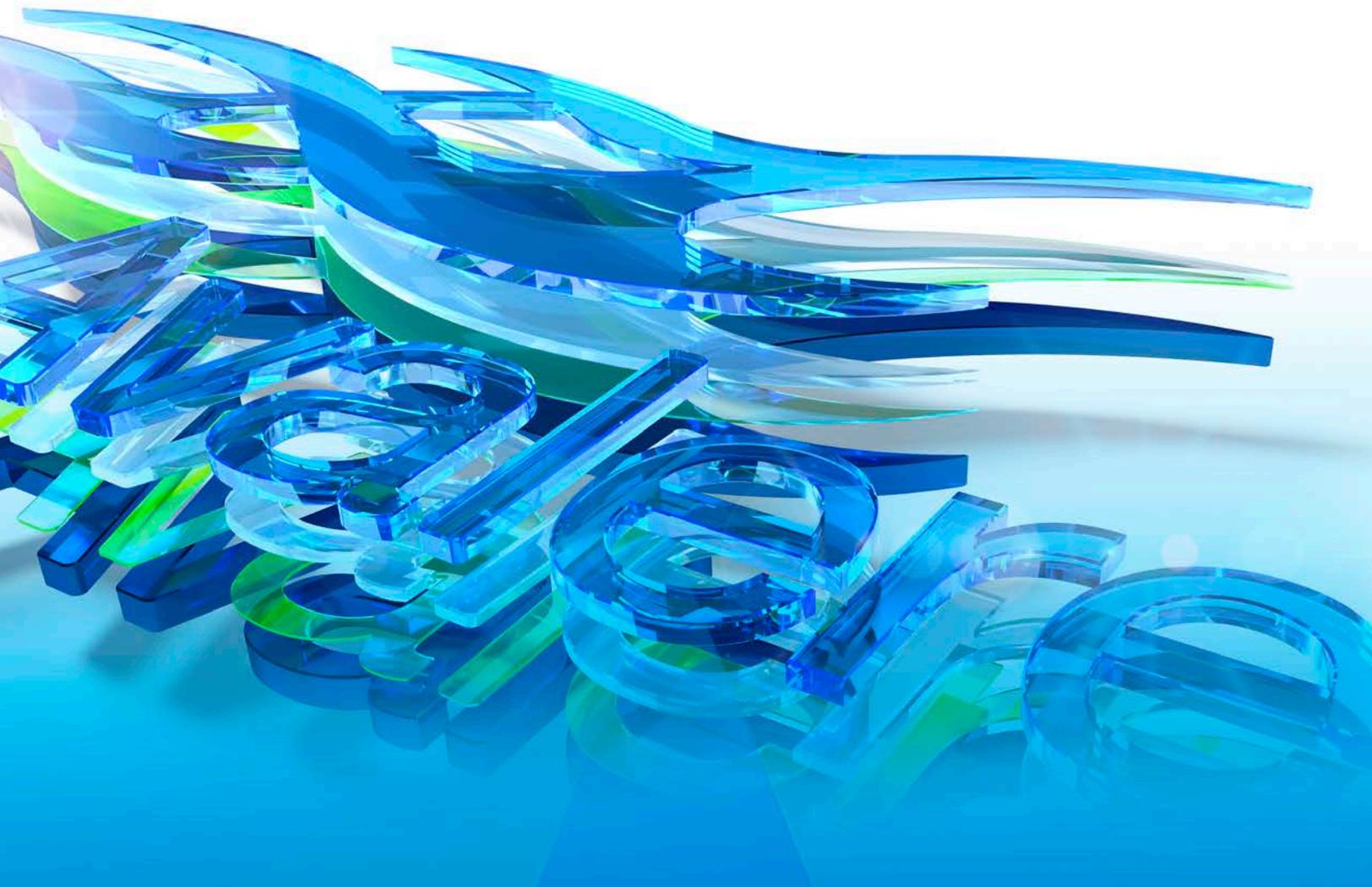


---

# The Patient-Perspective Value Framework: Short- and Long-Term Recommendations to Influence Value Assessment Methodology

Josh Seidman, Priya Gaur, Camille Boler | May 30, 2019



**Avalere Health**  
An Inovalon Company

1350 Connecticut Ave, NW  
Washington, DC 20036

T | 202.207.1300  
[avalere.com](http://avalere.com)

# Table of Contents

<b>Executive Summary</b>	<b>1</b>
<b>Glossary</b>	<b>3</b>
<b>Introduction</b>	<b>4</b>
<b>Short-Term Recommendations</b>	<b>7</b>
Focus Area 1 - Quality of Life	7
Focus Area 2 - Real-World Evidence and Guidance for Utilizing Patient-Reported Outcomes	13
Focus Area 3 - Patient Preferences	18
<b>Long-Term Recommendations</b>	<b>21</b>
Focus Area 1 - Patient-Centered Data Structure for Quality of Life & Real-World Data	22
Focus Area 2 - Evolution of FDA Requirements	28
Focus Area 3 - Increased Availability of Patient-Centered Data	32
<b>Appendix</b>	<b>39</b>

Avalere has published this paper to help existing and new value framework developers incorporate the patient voice into value assessment methodology and applications. We would like to acknowledge the American Society of Clinical Oncology (ASCO) and the National Comprehensive Cancer Network (NCCN) for their insights and feedback to Avalere and the PPVF Steering Committee during the development of this work.

# Executive Summary

In recent years, several organizations have developed and implemented value assessment frameworks, tools intended to support healthcare decision making at the population and individual level. Most value frameworks focus primarily on assessing clinical factors, such as effectiveness, safety, and toxicity. In addition to these factors, patients also place value on other key dimensions of value, such as patient preferences, other patient-centered outcomes, and patient and family costs considerations. The disconnect between the current state of value assessment methodology and diverse individualized perspectives on value has increasing importance as we evolve to a more value-based payment environment.

Although some value assessment developers do recognize the importance of patient preferences in treatment decision making, they often express practical concerns around the availability and rigor of patient-centered data and methodological challenges involved in personalized value assessment. Specific concerns include:

- Lack of routine collection of patient-centered data
- Minimal standardized guidance on how to best collect methodologically rigorous patient-centered data
- Limited use of tools (e.g., validated instruments) that could support collection of these data
- Potential bias associated with these data
- Little methodological experience with incorporation of patient preferences into value assessment methodology

Recognizing the growth in value frameworks that insufficiently incorporate the patient view, in Phase I of the Patient-Perspective Value Framework (PPVF) initiative, *Avalere/FasterCures* developed and released version 1.0 of the PPVF. In Phase II, we created an accompanying scoring methodology that provides further technical granularity to the Version 1.0 framework. Leveraging the PPVF domains, criteria, measures, and scoring methodology, *Avalere* convened a working group focused on improving the patient centeredness of value assessment. This paper explains how stakeholders involved in value assessment can adjust their frameworks to better incorporate patient-oriented aspects of value in both the short- and long-term.

Short-term Focus Areas:

1. Quality of Life (QoL) – Selection of validated QoL instruments to support collection of QoL data for value assessment calculations & treatment decision making
2. Real-World Evidence (RWE) and Guidance for Utilizing Patient-Reported Outcomes – Evaluation of the current state of RWE and identification of ways RWE can encourage incorporation of the patient perspective into value assessments

- 
3. Patient Preferences – Integration of patient preferences data at point of care and in value assessment methodologies

Long-term Focus Areas:

1. Patient-Centered Data Structure for QoL and Real-World Data (RWD) – Structural modifications to the existing patient-centered data architecture to promote RWD collection
2. Evolution of FDA Requirements – Identification of regulatory channels to advance appropriate aggregation of RWD
3. Increased Availability of Patient-Centered Data – Support of initiatives and tools that can promote the availability of cost, complexity of regimen, and patient preferences data

Within each focus area, we have developed consensus-based recommendations that researchers, regulatory bodies, providers, payers, and other stakeholders can pursue to expand the breadth of patient-centered data and to better reflect the patient perspective in such workstreams. To assure the practicality of these global recommendations, we have evaluated the recommendations in collaboration with 2 value assessment organizations, the American Society of Clinical Oncology (ASCO) and the National Comprehensive Cancer Network (NCCN). We look forward to engaging with other framework developers to adequately incorporate the patient voice into value assessment methodology and applications.

# Glossary

**Quality of Life:** A general concept that implies an evaluation of the effect of all aspects of life on general well-being.<sup>1</sup>

**Patient-Centered Outcome:** An outcome that is important to patients' survival, functioning, or feelings as identified or affirmed by patients themselves, or judged to be in patients' best interest by providers and/or caregivers when patients cannot report for themselves.<sup>2</sup>

**Patient Preference:** A statement of relative desirability or acceptability to patients of specified alternatives or choice among outcomes or other attributes that differ among alternative health interventions.<sup>3</sup>

**Patient-Reported Outcome (PRO):** 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 interpretation of the patient's response by a clinician or anyone else. A PRO can be measured by self-report or by interview, provided that the interviewer records only the patient's response. Symptoms or other unobservable concepts known only to the patient (e.g., pain severity or nausea) can only be measured by PRO measures. PROs can also assess the patient perspective on functioning or activities that may also be observable by others.<sup>4</sup>

**Real-World Data:** The data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources.<sup>5</sup>

**Real-World Evidence:** The clinical evidence regarding the usage and potential benefits or risks of a medical product derived from analysis of RWD.<sup>6</sup>

**Shared Decision-Making:** A process in which clinicians and patients work together to make decisions and select tests, treatments and care plans based on clinical evidence that balances risks and expected outcomes with patient preferences and values.<sup>7</sup>

---

<sup>1</sup> The U.S. Food & Drug Administration. Guidance for Industry, Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims. December 2009.

<sup>2</sup> The U.S. Food & Drug Administration. Patient-Focused Drug Development Glossary. June 2018.

<sup>3</sup> Ibid.

<sup>4</sup> Ibid.

<sup>5</sup> Ibid.

<sup>6</sup> Ibid.

<sup>7</sup> National Learning Consortium. Fact Sheet: Shared Decision Making. December 2013.

# Introduction

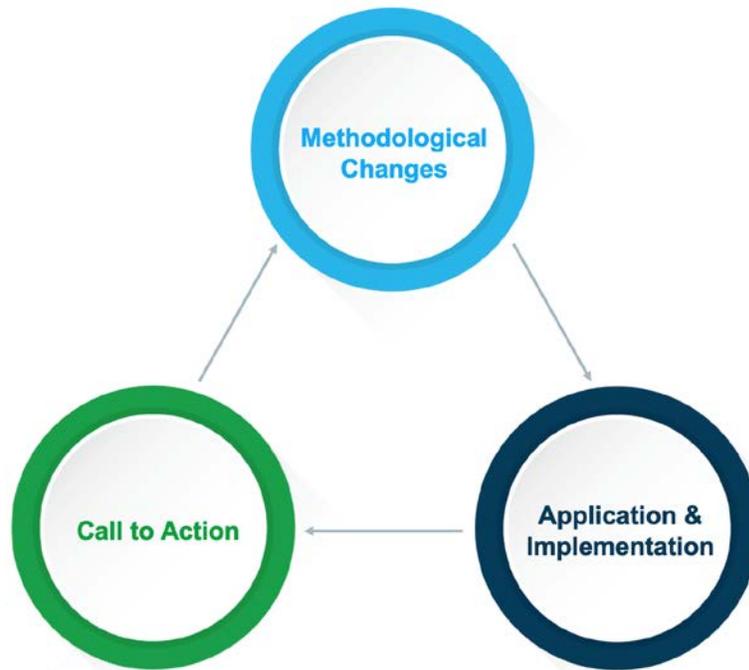
As part of Phase III of the Patient-Perspective Value Framework (PPVF) initiative, Avalere convened a Working Group with the objective of identifying technical recommendations to advance the patient centricity of value assessment frameworks and methodologies. The Working Group consists of representatives from the PPVF Steering Committee, the American Society of Clinical Oncology (ASCO), and the National Comprehensive Cancer Network (NCCN). Throughout Phase III, Working Group members have collaborated to better understand the patient-centered data ecosystem, identify areas where sufficient data exist to implement the PPVF's domains, criteria, and measures in the short-term, and identify longer-term opportunities that require a future call to action. Specifically, through this exploration, the Working Group has assessed examples of existing patient-reported data sources, methodological strategies for data collection, and potential approaches to evaluate real-world data for rigor and bias.

## Approach

To support the Working Group's recommendations, Avalere has conducted both primary and secondary research. Specific components of our approach include:

- Preliminary assessment of patient-reported data sources
- Interviews with patient organizations and other sponsors of patient-centered data
- Literature review of existing patient-reported data in general and a deeper dive within oncology
- Discussions with ASCO and NCCN to understand the methodology behind their respective frameworks and the challenges they faced in incorporating particular types of patient-oriented value assessments
- Evaluation of current patient-reported measurement instruments and rigor of data and data sources
- Identification and assessment of condition-agnostic and oncology-specific patient-reported outcomes (PRO) instruments

In completing this secondary and primary research, the Working Group has identified 3 ways to improve the patient-centered data landscape.



1. **Methodological Changes:** Potential changes to existing methodologies for assessing value of treatment options
2. **Application & Implementation:** Improved deployment of existing value frameworks in practice at the individual and/or population level
3. **Call to Action:** Areas for partnership with value framework sponsors to highlight and promote greater patient-centered data availability

Methodology, application, and call to action strategies can be leveraged together or independently to communicate areas for further development of value assessment methodologies.

## Summary of Recommendations

In this paper, the Working Group has identified short- and long-term recommendations to improve the patient orientation of value assessment methodologies and applications, as well as guide the longer-term integration of the patient voice in public and private value initiatives. Drawing on the 5 domains of the [Version 1.0 of the PPVF](#)<sup>8</sup> (including their affiliated criteria and measures) and the [PPVF Scoring Methodology](#)<sup>9</sup> (released in May of 2018), the Working Group has identified 3 areas of focus for short- and long-term recommendations.

<sup>8</sup> Version 1.0 materials can be found at the following link: <http://avale.re/2pJsAd1>

<sup>9</sup> The PPVF Scoring Methodology can be found at the following link: <http://avalere.com/expertise/providers/insights/avalere-releases-patient-perspective-value-framework-scoring-methodology-re>

## Short-Term Recommendations

- I. **Focus Area 1: Quality of Life** – Focuses on the selection of quality-of-life (QoL) instruments that are currently collectable and broadly utilized in the clinical literature. This section also pinpoints how QoL data can be leveraged to improve patient centricity in treatment decision making.
- II. **Focus Area 2: Real-World Evidence and Guidance for Utilizing Patient-Reported Outcomes** – Assesses the current state of real-world evidence (RWE) across all conditions, with a particular focus in oncology, and emphasizes how the monitoring and integration of such data can increase the patient voice in value assessments. Moreover, this section discusses the quality and rigor of RWE as well as the quality and applicability of PRO instruments leveraged in methodology and/or application.
- III. **Focus Area 3: Patient Preferences** – Calls for the inclusion of patient preferences data in value assessment methodologies. This section also outlines opportunities to better collect and consider patient preferences at the point-of-care application of value assessment frameworks through shared decision making.

## Long-Term Recommendations

- I. **Focus Area 1: Patient-Centered Data Structure for QoL and RWD** – Identifies opportunities and incentives to alter the architecture of patient-centered data collection to promote long-term, routine collection of rigorous RWD. This focus area also explores policy vehicles that can be leveraged to encourage such collection.
- II. **Focus Area 2: Evolution of FDA Requirements** – Evaluates current and future regulatory workstreams and initiatives to influence collection of RWD.
- III. **Focus Area 3: Increased Availability of Patient-Centered Data** – Explicates on avenues in which payers, providers, other stakeholders can expand collection of patient medical and non-medical costs. Moreover, this focus area discusses tools and resources that can advance the collection of complexity of regimen data. Finally, this focus area calls for the advancement of patient preference data collection at the individual and population level.



# Short-Term Recommendations to Influence Value Assessment Methodology

## Focus Area 1: Quality of Life

### Background

In the value assessment context, many organizations agree that PROs can be useful tools in assessing the value of healthcare options and determining how given options may impact QoL. However, value framework developers have also highlighted the challenges associated with incorporating PROs into routine use, including data availability and lack of standardization. In light of these challenges, the Working Group explored potential condition-agnostic and oncology-specific PROs, focusing on those that measure QoL and appear to be increasingly represented in the clinical trial literature.

**Recommendation 1:** Integrate the following PROs, which are increasingly represented in the clinical trial literature, into value assessment methodologies:

- 1) SF-12, SF-36
- 2) Patient-Reported Outcomes Measurement Information System-29 (PROMIS-29)
- 3) PROMIS Global Health Questionnaire
- 4) The MD Anderson Symptom Inventory (MDASI) Core Survey
- 5) The European Organization for Research and Treatment of Cancer Quality of Life of Cancer Patients (EORTC QLQ-C30)

Avalere has identified 5 validated instruments with substantial use in clinical trials that warrant consideration for incorporation into value assessment methodologies to increase the patient centricity of their approaches.

#### 1. SF-12 and SF-36:

- a. Developed by RAND as a result of their multi-year, multi-site, Medical Outcomes Study, the SF-12 and SF-36 measure 8 dimensions of QoL in 12 or 36 questions respectively.<sup>10</sup> These condition-agnostic surveys have been validated across numerous conditions and populations and have also served as legacy tools for the development and validation of other instruments including certain PROMIS questionnaires. The SF-36's validated sister tool, SF-12, consists of a subset of SF-36 items measuring the same 8 QoL dimensions. Although the SF-36 provides more depth in the evaluation of QoL, either version would provide valuable QoL

---

<sup>10</sup> RAND HealthCare. "36-Item Short Form Survey (SF-36)," [https://www.rand.org/health-care/surveys\\_tools/mos/36-item-short-form.html](https://www.rand.org/health-care/surveys_tools/mos/36-item-short-form.html).

insights. The SF-36 has been used in more than 1000 peer reviewed articles and has been identified as the most frequently used PRO in clinical trials.<sup>11</sup>

- b. The SF-12 and SF-36 can be completed in 2-10 minutes, dependent on which survey is taken.<sup>12, 13</sup> The original SF-36 is publicly available, and free of charge. SF-36v2, which offers increased range and precision in certain item scales, an easier-to-use format, and improved item wording, can be acquired through a small licensing fee.

## 2. PROMIS-29:

- a. Established in 2004, the National Institute of Health developed PROMIS, a set of person-centered measurements evaluating physical, mental, and social health. To date, PROMIS includes over 300 instruments for general or chronic condition use. One of the most utilized, the PROMIS-29, assesses 7 QoL dimensions and has been validated for use in numerous therapeutic areas and general use.<sup>14</sup>
- b. The PROMIS-29 is generally completed in 10-15 minutes.<sup>15</sup> PROMIS tools are publicly available, free to use, and can be administered in multiple ways.<sup>16</sup>

## 3. PROMIS Global Health Questionnaire:

- a. Another commonly used PROMIS questionnaire, the PROMIS Global Health Questionnaire, is more concise, being comprised of 10 questions measuring 2 QoL dimensions.<sup>17</sup> Notably, the Center for Medicare & Medicaid Services (CMS) includes the PROMIS Global Health Questionnaire in its Measures Inventory Tool, a repository of measures that CMS uses to promote healthcare quality and quality improvement.<sup>18</sup> This questionnaire has also been used and validated in diverse settings and populations across numerous conditions.
- b. The PROMIS Global Health Questionnaire can be taken in ~2 minutes.<sup>19</sup> PROMIS tools are publicly available, free to use, and can be administered in multiple ways.<sup>20</sup>

## 4. MDASI Core Survey:

---

<sup>11</sup> Scoggins, JF and Patrick, DL. "The Use of Patient-Reported Outcomes Instruments in Registered Clinical Trials: Evidence from ClinicalTrials.gov." Contemporary Clinical Trials. July 2009. 30(4): 289-92.

<sup>12</sup> National Council for Osteopathic Research. "SF-36." <https://www.ncor.org.uk/wp-content/uploads/2013/01/SF-36.pdf>.

<sup>13</sup> Australian Health Outcomes Collaboration. "Instrument Review: SF-12® Health Survey (Version 1.0)." <https://ahsri.uow.edu.au/content/groups/public/@web/@chsd/documents/doc/uow132412.pdf>.

<sup>14</sup> "PROMIS List of Adult Measures." HealthMeasures. [http://www.healthmeasures.net/index.php?option=com\\_content&view=category&layout=blog&id=113&Itemid=808](http://www.healthmeasures.net/index.php?option=com_content&view=category&layout=blog&id=113&Itemid=808).

<sup>15</sup> "PROMIS-29." [https://www.aci.health.nsw.gov.au/data/assets/pdf\\_file/0003/402087/Overview-of-the-PROMIS-29\\_EH-140817.pdf](https://www.aci.health.nsw.gov.au/data/assets/pdf_file/0003/402087/Overview-of-the-PROMIS-29_EH-140817.pdf).

<sup>16</sup> PROMIS Obtain & Administer Measures." HealthMeasures. <http://www.healthmeasures.net/explore-measurement-systems/promis/obtain-administer-measures>

<sup>17</sup> "PROMIS List of Adult Measures." HealthMeasures.

<sup>18</sup> Center for Medicare & Medicaid Services. CMS Measures Inventory. <https://www.cms.gov/Medicare/Quality-Initiatives-Patient-Assessment-Instruments/QualityMeasures/CMS-Measures-Inventory.html>

<sup>19</sup> Shanthik, Kasturi et al. "Feasibility, Validity, and Reliability of the 10-item Patient Reported Outcomes Measurement Information System Global Health Short Form in Outpatients with Systemic Lupus Erythematosus. The Journal of Rheumatology. February 2018.

<sup>20</sup> PROMIS Obtain & Administer Measures." HealthMeasures. <http://www.healthmeasures.net/explore-measurement-systems/promis/obtain-administer-measures>

- a. This oncology-specific, multi-symptom PRO instrument assesses the severity of symptoms and resulting interferences with daily living for cancer patients. This core MDASI measurement consists of 13 symptom items and 6 interference items, yielding a holistic 19-item questionnaire. This survey can be broadly applied to various cancer and tumor types, can be administered in many formats, and has been translated and validated in over 40 languages. MDASI results are provided on a 0-10 scale, prompting patient-friendly use and understanding of their results.<sup>21</sup>
- b. Administration of the MDASI Core Survey can take between 1 and 5 minutes, dependent on mode of administration.<sup>22</sup> Use of the MDASI Core survey is subject to licensing fees and a \$100 processing fee dependent on type and extent of use, setting, and research sponsor.<sup>23</sup>

## 5. EORTC QLQ-C30:

- a. Developed to evaluate QoL for cancer patients, the EORTC QLQ-C30 serves as 1 of the 4 core tools developed by the EORTC. This multi-dimensional, 30-item questionnaire has been translated into over 100 languages and has been validated across a variety of settings and different cancer and tumor types. Annually, the EORTC QLQ-C30 has been used in more than 5,000 studies worldwide.<sup>24</sup>
- b. Respondents generally complete the EORTC QLQ-C30 in 10-15 minutes.<sup>25</sup> Commercial use of the EORTC QLQ-C30 requires a Commercial User Agreement and a fee dependent on the number of patients in the study.<sup>26</sup>

Each of the 5 instruments captures the patient voice in its own way, aligning with the overall PPVF and the goal of Phase III: Longer-term incorporation of the patient voice in public and private value initiatives. Specifically, all 5 instruments map to the QoL criterion's measures as depicted in Diagram 1.

<sup>21</sup> The University of Texas, MD Anderson Cancer Center. "The MD Anderson Symptom Inventory." <https://www.mdanderson.org/research/departments-labs-institute/departments-divisions/symptom-research/symptom-assessment-tools/md-anderson-symptom-inventory.html>

<sup>22</sup> The M.D. Anderson Symptom Inventory User Guide, Version 1. 2016. [https://www.mdanderson.org/documents/Departments-and-Divisions/Symptom-Research/MDASI\\_userguide.pdf](https://www.mdanderson.org/documents/Departments-and-Divisions/Symptom-Research/MDASI_userguide.pdf).

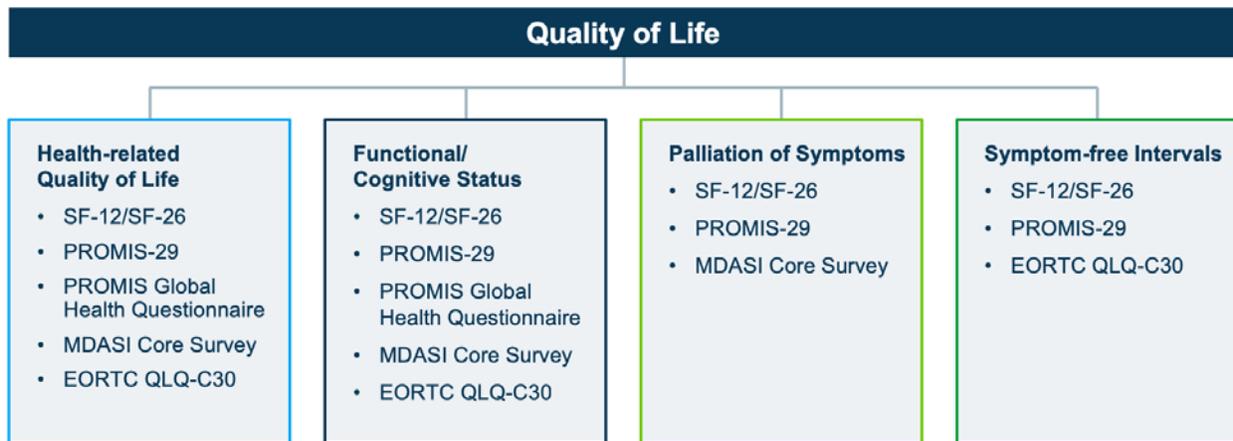
<sup>23</sup> Ibid.

<sup>24</sup> The European Organization for Research and Treatment of Cancer. "Quality of Life of Cancer Patients." <https://qol.eortc.org/questionnaire/eortc-qlq-c30/>

<sup>25</sup> The European Organization of Research and Treatment of Cancer. Quality of Life-Frequently Asked Questions. <https://qol.eortc.org/faq/?q=faq&tid=15>.

<sup>26</sup> The European Organization for Research and Treatment of Cancer. "Quality of Life of Cancer Patients."

**Diagram 1: Mapping of PRO Instruments to the PPVF**



**Representation in Clinical Settings and Published Literature: Condition-Agnostic Results**

The identified PRO tools have all been used to help collect, measure, and use patient-reported information in interventional studies, observational studies, patient registries, and published literature across multiple condition areas. The following table showcases each tool’s condition-agnostic representation in clinical settings and published literature.

**Table 1: Condition-Agnostic Representation of PRO Instruments in Clinical Settings and Published Literature**

	Representation in RCTs	Representation in RWE (Observational Studies)	Representation in RWE (Patient Registries)	Representation in Published Literature
<b>Short Form Surveys</b>	2713 studies (307 with results)	372 studies (17 with results)	41 patient registries (none with results)	492 published studies (65 clinical trials published)
<b>PROMIS-29</b>	25 studies (1 study with results)	5 studies (none with results)	1 patient registry (no results)	56 published studies (7 clinical trials published)
<b>PROMIS Global Health Questionnaire</b>	44 studies (7 with results)	1 study (no results)	N/A	80 published studies (8 clinical trials published)
<b>MDASI</b>	18 studies (5 with results)	7 studies (none with results)	N/A	112 published studies (23 clinical trials published)
<b>EORTC-QLQ-C30</b>	459 studies (83 with results)	58 studies (1 with results)	6 patient registries (none with results)	1383 published studies (323 clinical trials published)

Table 1 illustrates the prevalence of these 5 validated instruments in recent clinical settings and published literature. Within clinical literature, the SF-12/SF-36 and the EORTC-QLQ-C30 have been used extensively over the past 5 years, serving as a primary or secondary outcome measure for more than 3,000 randomized control trials (RCTs). All 5 instruments have been broadly used in over 2,100 clinical trials with published results. Specifically, the SF-12/SF-36 and the EORTC-QLQ-C30 have been utilized in over 1,800 published studies. Interestingly, nearly 21% of those studies are published clinical trials.

It is key to note that just over 9% of those interventional studies are completed and have produced results. This suggests that that substantially more patient-reported data will be available in the near future.

A review of RWE shows higher utilization of the SF-12/SF-36 and the EORTC QLQ-C30 when compared to the other 3 instruments. The SF-12/SF-36 and EORTC QLQ-C30 have been included in 477 RWE sources in the past 5 years while the PROMIS-29, PROMIS Global Health Questionnaire, and MDASI core survey have been incorporated into 14. However, there is still a strong use of PRO instruments in RWE at large.

### **Representation in Clinical Settings and Published Literature: Oncology-Specific Results**

The SF-12/SF-36, PROMIS Global Health Questionnaire, and PROMIS-29 are all condition-agnostic tools, but each has been used significantly in oncology at the general and cancer/tumor-specific level, as portrayed in Table 2.

**Table 2: Oncology-Specific Representation of PRO Instruments in Clinical Settings and Published Literature**

	Representation in RCTs	Representation in RWE (Observational Studies)	Representation in RWE (Patient Registries)	Representation in Published Literature
Short Form Surveys	253 studies (30 with results)	37 studies (1 study with result)	1 patient registry (no results)	44 published studies (6 clinical trials published)
PROMIS-29	4 studies (none with results)	1 study (no results)	N/A	9 published studies (no clinical trials)
PROMIS Global Health Questionnaire	10 studies (1 with results)	N/A	N/A	28 published studies (2 clinical trials published)
MDASI	18 studies (5 with results)	6 studies (none with results)	N/A	111 published studies (23 clinical trials published)
EORTC-QLQ-C30	435 studies (81 with results)	53 studies (1 with results)	4 patient registries (none with results)	1345 published studies (319 clinical trials published)

When compared to its condition-agnostic use, the representation of the SF-12/SF-36, PROMIS Global Health Questionnaire, and PROMIS-29 in oncology-specific RCTs is relatively low; nearly 10% of oncology-specific RCTs use 1 of the 3 respective instruments. This suggests an opportunity for inclusion of the SF-12/SF-36, PROMIS-29, and PROMIS Global Health Questionnaire in ongoing and future oncology-specific patient-centered RCTs. In addition, over 450 oncology-specific interventional studies conducted in the past 5 years include either the MDASI Core survey or the EORTC QLQ-C30. Use of the 5 PRO instruments in RWE shows less frequency as only 102 studies have used 1 of the tools in RWE research. Only 13% of all oncology-specific published literature uses SF-12/SF-36, PROMIS-29, or the PROMIS Global Health Questionnaire. The MDASI Core survey and the EORTC QLQ-C30 have nearly identical use in oncology as general use with 97% of published studies researching within oncology.

**Recommendation 2: Integrate the use of QoL data into clinical settings to help support patient-centered treatment decision making**

As a first step to better understand the availability of patient-reported real-world data (RWD), the Working Group completed a preliminary assessment of 43 RWD sources across all condition types. After mapping data elements collected from these 43 sources to the PPVF's domains, criteria and measures, the Working Group observed that QoL data appear to be regularly collected among data sources included in the sample. Specifically, the Working Group observed that 28 of the 43 sources collected QoL data; many of these sources were focused in oncology.

These findings suggest there may be an opportunity to further investigate how patient-reported data capturing QoL may be integrated into value assessment; specifically, the use of the 5 outlined PRO instruments may be utilized to guide the collection of rigorous QoL data to enhance value assessment methodologies. It is also imperative that these data be considered in clinical decision making because many patients emphasize the importance of this criterion in treatment decisions. One Cancer Support Community study found that 80% of breast cancer patients indicated that quality of life mattered “very much” when making treatment decisions.<sup>27\*</sup> Furthermore, the study found that the majority of both non-metastatic and metastatic patients expressed that quality of life had a greater impact on their treatment decision than other prioritized considerations, such as length of life, impact on family and financial cost of care.<sup>28</sup> Though these data do not necessarily reflect the values of all cancer patients, they do demonstrate the importance of considering QoL within oncology. This study highlights the strong prioritization of QoL data for patients when making a clinical decision. Thus, the integration of QoL data into clinical treatment decisions can help patients make more informed, personally relevant decisions.

---

*Evaluation of the 5 QoL instruments is a preliminary and overarching assessment of representation in interventional studies, observational studies, patient registries, and published literature. These results are not intended to holistically capture all use of the Short Forms surveys, PROMIS-29, the PROMIS Global Health Questionnaire, MDASI, and EORTC QLQ-C30 in clinical and literature settings.*

\* The Cancer Support Community registry is composed of 14,000 cancer patients. On average, registry participants are predominantly female and are somewhat educated.

<sup>27</sup> Buzaglo, Joanne S, et al. “Non-metastatic and Metastatic Breast Cancer Patients’ Priorities When Considering a Treatment Decision.” Poster presented at the San Antonio Breast Cancer Symposium; 2016, Durham, 2018.

<sup>28</sup> Ibid.

## Focus Area 2: Real-World Evidence and Guidance for Utilizing Patient-Reported Outcomes

### Current State of Real-World Evidence

Numerous organizations have recognized the importance of RWE and its increasing importance in regulatory decision making, shared decision making, and quantitatively describing the patient voice. The Food and Drug Administration (FDA) recently outlined a framework for their Real-World Evidence Program, focusing on how RWD and RWE can potentially be used to support regulatory decision making regarding product effectiveness and safety, and how this use can support changes to FDA labeling.<sup>29</sup> The framework identifies multiple program items that the FDA intends to actualize, such as, “review and, where applicable, publish guidance on potential gaps in RWD sources and strategies to address them” further highlighting the positive implications of RWE use in different settings.<sup>30</sup> This recent publication exemplifies the ongoing movement towards the improved quality and usability of RWE and how cross-stakeholder groups can better leverage such data.

**Recommendation 1:** Actively monitor the ongoing development of oncology RWE sources in order to identify specific areas for incorporation of patient-centered RWE elements into value assessment methodology and point-of-care framework application.

Given the evolving state of RWE in oncology as well as the learnings from the Working Group’s review of patient-reported RWD sources, value assessment organizations have an opportunity to actively monitor cancer patient-reported RWE sources that align to the data elements articulated in the PPVF.

Data collected through RCTs provide great insight on product or therapy efficacy. However, these results are limited in their ability to holistically assess value due to their limitations in capturing patient preferences, values, and the broader patient experience. As such, RWE presents a critical opportunity to integrate QoL and other forms of patient-reported data into value assessment methodology and frameworks.

Sources of RWE differ in approach and data elements collected. When brought together, this diversity in data addresses several PPVF domains, criteria and measures. The following tables describe different patient registries and non-registry patient data sources that collect patient-reported data aligning to different PPVF domains and criteria.

---

<sup>29</sup> U. S. Food & Drug Administration. “Framework for FDA’s Real-World Evidence Program.” December 2018. [www.fda.gov](http://www.fda.gov).

<sup>30</sup> Ibid.

**Table 3: Patient Registries**

	Description	PPVF Domains, Criteria, Measures Collected
Cancer Support Community Cancer Experience Registry	<p>The Cancer Support Community’s (CSC) Cancer Experience Registry allows cancer patients and caregivers to share their experiences, take surveys, access resources, and identify issues that affect their lives. CSC’s report findings derived from trends in their registry are based on patient perceptions of different aspects of their cancer treatment course. Topics of interest include: cancer-related distress; quality of life; treatment decision-making and planning; side effects and symptom management; clinical trials; financial toxicity; and work-related experience. The Cancer Experience Registry consists of more than 12,000 participants representing over 45 cancer types. Nevertheless, CSC continues active outreach and recruitment to increase registry participation and create a greater collective voice reflecting on the cancer journey.</p> <p>In addition to the ~12,000 patients in the registry, CSC has robust data on ~3,000 patient QoL (spiritual, physical, emotional, social, etc.) stemming from their survey asking questions related to psychosocial functioning, decision making, relationships with caregivers, and more. Recent CSC focus now emphasizes the collection of patient value data to help identify unmet needs throughout the treatment decision making process. CSC does note that their main challenges in their data collection efforts are identifying people to add to the registry, ensuring participants finish their registry survey, and diversifying their registry population.</p>	<ul style="list-style-type: none"> <li>• Patient Values</li> <li>• Patient Needs</li> <li>• Patient Financial Trade-Offs</li> <li>• Quality of Life</li> <li>• Safety/Side Effects</li> <li>• Medical Out-of- Pocket (OOP) Costs</li> <li>• Non-Medical Costs</li> </ul>
Lung Cancer Registry	<p>The Lung Cancer Registry houses detailed, self-reported medical information about lung-cancer patients. Specific data elements are not disclosed on their website; however, the patient survey instrument is publicly available. Survey sections/topics include registered user information, symptoms, non-lung cancer treatment, diagnosis, other cancer history, testing, and current and prior treatment- therapy. The general questions section gathers more information about the patient (e.g. access to supportive care, use of education material, health insurance, occupations, etc.).</p>	<ul style="list-style-type: none"> <li>• Quality of Life</li> <li>• Complexity of Regimen</li> <li>• Safety/Side Effects</li> <li>• Medical OOP Costs</li> </ul>

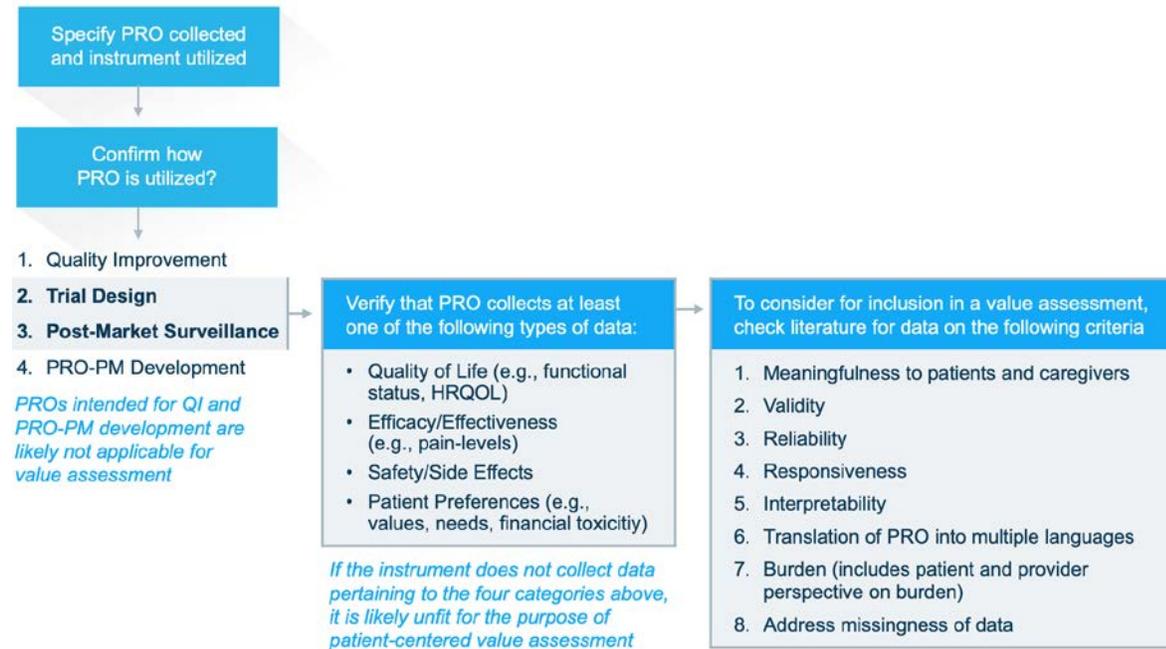
**Table 4: Non-Registry Patient-Centered Data Sources**

	Description	PPVF Domains, Criteria, Measures Collected
CancerCare	<p>CancerCare's patient data revolves around patient access and engagement in their cancer treatment course. CancerCare currently has patient data such as, basic demographic information, disease type, and patient/caregiver information for up to 195,000 patients with data dating back to 7 years ago. Additionally, CancerCare has evidence on patient finances and current medication from their financial services programs. As published, the CancerCare Patient Access and Engagement Report provides data on more than 3000 patients' experiences, opinions and priorities throughout the continuum of care. Current challenges for CancerCare data collection are threefold: limited patient comprehension of their diagnosis, need for focus on actual patient engagement versus data collection, and not capturing all relevant patient data.</p> <p>Notably, CancerCare will be launching a new data collection system, aiming to collect more detailed information regarding the patient experience. This new data collection effort is likely to fill in gaps through client follow-up surveys and more detailed responses.</p>	<ul style="list-style-type: none"> <li>• Patient Values</li> <li>• Patient Needs</li> <li>• Patient Goals/expectations</li> <li>• Patient Financial Trade-offs</li> <li>• Quality of Life</li> <li>• Medical OOP Costs</li> <li>• Non-Medical Costs</li> <li>• Future Costs of Care</li> </ul>
PatientsLikeMe	<p>PatientsLikeMe is a platform for patients to directly recount their healthcare experiences and regimen and track patient progress throughout the healthcare decision-making process. Users are able to create a profile disclosing their diagnoses, treatment regimens, side effects, and their experiences with other aspects of their treatment course. This resource currently houses data on more than 630,000 people living with over 2,800 types of conditions.</p>	<ul style="list-style-type: none"> <li>• Patient Values</li> <li>• Quality of Life</li> <li>• Efficacy &amp; Effectiveness</li> <li>• Complexity of Regimen</li> <li>• Safety/Side Effects</li> </ul>

**Recommendation 2:** Utilize a protocol for evaluating PRO instruments and determining whether PRO data is suitable for inclusion in value assessment methodology.

PROs collected in RWE sources may serve a variety of purposes. As such, it will be imperative for value assessment organizations to follow a protocol, as suggested in Diagram 2, for establishing if a PRO is fit for use in value assessment methodology and determining that it meets a set of patient-centered and methodological criteria, including validation and rigor (see Appendix A for more detail).

**Diagram 2: Protocol To Determine Whether PRO Is Fit for Use**



**Recommendation 3:** Consider opportunities to balance RWE as a complement to RCTs in order to more holistically capture the patient experience.

RCTs have the advantage of relying on a largely standardized methodological structure across various conditions and outcomes. Clinical trial results are also increasingly leveraged and in a more standardized fashion because of established guidelines and best practices by influential organizations like the FDA. However, RCTs have a variety of limitations regarding: homogeneity of populations; narrow assessment of outcomes (often lacking some of the outcomes that matter most to patients); lag time in converting research to available knowledge; and limited external validity beyond the narrow experimental conditions of efficacy testing. These limitations threaten our ability to understand in a timely way the real-world effectiveness of healthcare options relative to patients’ priorities. Data collected from RWE sources can provide meaningful considerations and evaluation data, particularly across those domains, criteria, and measures that matter to patients and caregivers. Combining different types of data sources can help us to better triangulate the answers as to the true value of various healthcare options.



RWE can help to contextualize and more comprehensively assess patient experiences and values by capturing information outside of the standardized structure of RCTs. For example, an RCT's primary outcome may measure a change in symptom-free intervals or response rates. Although this information is valuable in assessing clinical efficacy, it does not incorporate these results into the broader patient experience. For example, a patient's treatment goals may suggest he or she values QoL over specific efficacy outcomes or prefer one clinical efficacy outcome over another (e.g., progression-free survival compared to symptom-free intervals). The utilization of RWE may be able to answer this question by assessing additional patient-centered elements.

Moving forward, value assessment organizations must seek to integrate processes to evaluate the rigor and relevance of RWE such that it can be utilized alongside RCT data. Several organizations have presented frameworks to support this endeavor. For example, the Center for Medical Technology Policy has developed the RWE Decoder, a spreadsheet-based assessment tool that positions healthcare decision makers to review and evaluate existing studies and evidence for both rigor and relevance. Drawing on the RWE Decoder, the PPVF Scoring Methodology articulates a process by which data from different types of studies (e.g., RCT, meta-analysis, RWE) can be synthesized, adjusted based on the rigor and sources of biases, and utilized to inform a more holistic perspective on value assessment.

## Focus Area 3: Patient Preferences

### Background

As a required product of the 21<sup>st</sup> Century Cures Act and part of the FDA commitments established under the Prescription Drug User Act (PDUFA VI), the Patient-Focused Drug Development FDA guidance glossary outlines standardized nomenclature and terminologies related to patient-focused medical product development. This guidance defines “patient preference” as a statement of the relative desirability or acceptability to patients of specified alternatives or choice among outcomes or other attributes that differ among alternative health interventions.<sup>31</sup> Similarly, the Patient-Centered Outcomes Research Institute (PCORI) has established terminology to help standardize its research methodology and protocols. As such, PCORI defines “patient preferences” as the relevance to patients and clinicians in making informed health decisions, and priorities in the National Strategy for quality care.<sup>32</sup> Further, PCORI acknowledges the need to consider potential differences in the effectiveness of healthcare treatments, services and items, including on the basis of quality of life preferences. As established, both definitions can be employed by patients, caregivers, value framework sponsors, and other relevant parties to help improve treatment decision making in clinical settings.

In developing methodologies and deploying frameworks at the point of care, value assessment organizations must consider opportunities to elicit and consider patients’ individual preferences. To date, routine incorporation of patient preferences into clinical practice and decision making remains limited. Research led by the Patient Advocate Foundation shows that cancer patients’ healthcare-related preferences vary greatly among individuals, based on the progression of the disease, stage of life, and demographics.<sup>33</sup> Qualitative research conducted by *CancerCare*, found that cancer patients want their providers to understand and appreciate the effect treatment has on their lives, such as on their jobs, financial status, family and household responsibilities, access to transportation, and significant upcoming plans.<sup>34</sup> However, a survey with 3,000 American adults with cancer found that patients do not receive the information they need to make healthcare decisions based on their personal preferences and values.<sup>35</sup>

Variability in patients’ individual treatment preferences, needs, and values underscores the need to elicit patient preferences and incorporate them into value assessment instead of excluding or considering these data separately. Patients and physicians can also use patient preference data as part of treatment decision-making conversations, highlighting another way to leverage such data to incorporate patient preferences at the point of care. To that end, value framework developers can develop processes to ensure that patient preferences data are integrated into the development of assessment methodologies and/or alongside the application of their frameworks at the point of care.

---

<sup>31</sup> The U.S. Food & Drug Administration. Patient-Focused Drug Development Glossary. June 2018.

<sup>32</sup> The Patient Protection and Affordable Care Act (Consolidated), Compilation of Patient Protection and Affordable Care Act: Extracted Sections Concerning Patient-Centered Outcomes Research and the Authorization of the Patient-Centered Outcomes Research Institute." June 9, 2010

<sup>33</sup> Alan Balch, "The Roadmap to Consumer Clarity in Health Care Decision Making: Making Person-Centered Care a Reality," (Hampton, VA: The Patient Advocate Foundation, 2017).

<sup>34</sup> CancerCare, "Patient Values Initiative: The Many Voices of Value, a CancerCare Focus Group Assessment." New York, 2017.

<sup>35</sup> "CancerCare Patient Access and Engagement Report." New York, 2016.

## Recommendation 1: Embed patient preference as a criterion in existing value assessment methodologies to generate more personalized value calculations.

Many value frameworks have not included patient preferences in their overarching methodological equations for determining value, citing an overall lack of patient preferences data and limited standardization of these data. However, patients' individual values, needs, and goals affect how they perceive the value of healthcare options; therefore, value assessment should reflect that variation. Otherwise methodologically sound value assessment that fails to acknowledge differences in patient prioritization of outcomes will result in a precise answer to the wrong question.

Various sources of patient preference data have helped inform patients' decision-making processes. In a study on patient priorities in cancer care, the Cancer Support Community found that quality of life, length of life, impact on family, and financial cost of care were determining factors in their treatment decisions.<sup>36</sup> Specifically, 93% of participants remarked that quality of life mattered "very much" or "quite a bit" to them in treatment decision making.<sup>37</sup> Additionally, the CancerCare Patient Access and Engagement Report found that at least 39% of patients were "very or extremely concerned" about taking care of their family, at least 34% were "very or extremely concerned" about treatment convenience for themselves and their families, and 37% were "very or extremely concerned" about participating in activities that they enjoyed.<sup>38</sup> As such, the integration of this type of patient preferences data, especially related to quality of life, into value assessments may help yield a more patient-centered output from different value frameworks.

Patients also prioritize and heavily consider various patient preference data when it relates to complexity of a regimen. For example, in the PrefMab randomized trial evaluating patient preferences towards Rituxan Hycela (subcutaneous-SC) compared to Rituxan (intravenous-IV), researchers found that patient preferences can differ based on complexity of regimen, 1 of the PPVF criteria in the patient-centered outcomes domain. Using the Rituximab Administration Satisfaction Questionnaire, investigators found that the majority of patients (77%) preferred Rituxan Hycela (SC) over Rituxan (IV), citing less time in the clinic during administration as the most common reason.<sup>39</sup> On the other hand, few patients (11%) preferred Rituxan (IV) over Rituxan Hycela (SC), indicating more comfort during administration as the most common reason. Ultimately, the FDA recognized these patient preferences findings as critical and included the PrefMab study results on the FDA label for Rituxan Hycela. This study affirms that patients' values and preferences regarding complexity of a regimen can affect the value they place on different treatment options. Moreover, learnings from this study may guide the path for future patient-centered data integration into regulatory decision making.

---

<sup>36</sup> Buzaglo J.S., Miller, M.F., Longacre, M.L. "Cancer Patients' Priorities When Considering a Treatment Decision." Poster presented at the 8<sup>th</sup> Biennial Cancer Survivorship Research Conference: Innovation in a Rapidly Changing Landscape; 2016, Washington, DC.

<sup>37</sup> Ibid.

<sup>38</sup> CancerCare. "CancerCare Patient Access & Engagement Report." New York: CancerCare; 2016.

<sup>39</sup> Hoffmann-La Roche. "A Study of Participant Preference with Subcutaneous Versus Intravenous MabThera/Rituxan in Participants with CD20+ Diffuse Large B-Cell Lymphoma or CD20+ Follicular Non-Hodgkin's Lymphoma Grades 1, 2 or 3a." National Institutes of Health, U.S. National Library of Medicine. 2018.

As suggested through the Cancer Support Community research and findings from the PrefMab study, patient preferences including, but not limited to, QoL, costs, and complexity of regimen can play an instrumental role in how patients make decisions about treatments. Failure to incorporate patient preference data may therefore lead to an incomplete assessment of value, with conclusions that do not reflect the domains of value most important to patients.

**Recommendation 2: Develop, adapt, or invest in validated shared decision-making (SDM) tools that support the collection of patient preferences to inform how value assessment frameworks are applied at the point of care.**

As noted above, the regular collection and integration of patient preferences into clinical practice or decision making remains a challenge in oncology. Use of appropriate, validated SDM tools can support the application of value assessment at the point of care. Recently, a multi-stakeholder collaborative articulated best practices that can be applied to the development of patient-centered SDM tools and approaches.<sup>40</sup> These best practices include:

1. Engaging diverse stakeholders
2. Developing and validating an evidence-based SDM tool
3. Creating a roadmap for implementation

The collaborative found that current patient preference elicitation instruments are not sufficient to truly assess the values, needs, and preferences of individual cancer patients. To that end, the collaborative developed a novel patient preference elicitation tool with the input of patients that captures key domains of patient preferences, needs, and values. This tool has also been embedded in the provider-facing portion of the PPVF Preparation for SDM tool, which is intended for patients with advanced breast cancer.

The Working Group recommends that value assessment organizations integrate these types of patient preference elicitation tools or use them alongside value frameworks value assessment framework methodology. Specifically, value assessment organizations should develop guidance for providers utilizing their frameworks at the point of care on how to embed validated patient preference tools – like the PPVF Preparation for SDM tool or the shorter provider-facing patient preferences elicitation tool developed by the aforementioned collaborative – that align to the specific components of their frameworks. Where tools do not exist, value assessment organizations should invest in the development and validation of shared decision-making tools, in alignment with the process articulated by the collaborative.

Moreover, the Working Group recommends ongoing exploration into tools, such as Dartmouth's [CollaboRATE](#), that may help guide the provision of high-quality SDM. The ability to quantify and gauge the engagement and effectiveness of the integration of patient values into SDM is essential to the long-term development, implementation, and evaluation of SDM. So long as patient preferences are fully integrated in conversations between providers and patients, the use of an accountability tool may be deployed at different points of the treatment decision-making spectrum.

---

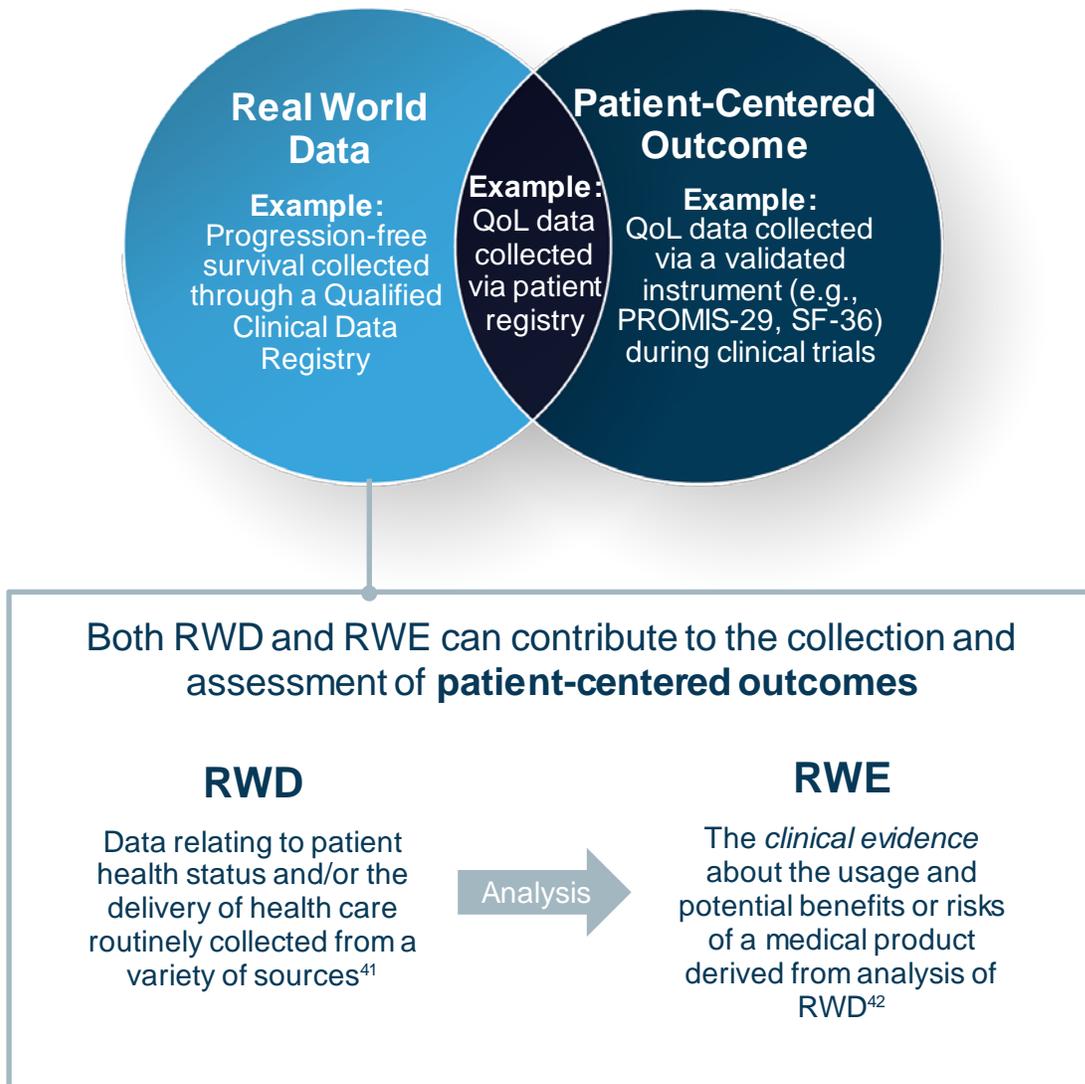
<sup>40</sup> Rocque et al. Engaging Multidisciplinary Stakeholders to Drive Shared Decision-Making in Oncology. *Journal of Palliative Care*. 2019. 34(1): 29-31

# Long-Term Recommendations To Influence Value Assessment Methodology

## Overview: Real World Data (RWD), Real World Evidence (RWE), and Patient-Centered Outcomes

The use of RWD, RWE, and patient-centered outcomes can all be used to advance the broader patient-centered data landscape and support the overall routine collection of these data. Nonetheless, differences and similarities among the 3 elements drive their respective purposes and appropriate use. The graphic below depicts the relationship between RWD, RWE, and patient-centered outcomes.

Diagram 3: Overview of RWD, RWE and Patient-Centered Outcomes



## Focus Area 1: Patient-Centered Data Structure for QoL and RWD

### Background

As outlined in the short-term recommendations, RWE has the potential to provide meaningful data on the domains of value that matter most to patients. However, to date, use of RWD are not as widespread as other types of data (e.g., those collected through randomized controlled trials). One key limitation is the lack of accepted standards in the design, architecture, and analysis of RWD. The lack of standards in turn makes it difficult for researchers and life sciences companies to routinely collect RWD. One literature review that compared 9 standards/guidelines intended to assist the standardization of observational studies found 14 mutually identified principles. Yet, 12 of these elements disagreed in approach.<sup>43</sup> Moreover, the extent of detail and degree to which each guideline varied.<sup>44</sup> Recognizing that each standard/guideline was created for different audiences, this study still highlights the lack of alignment across standards created for the same purpose: assist the establishment of standardized, routine collection of patient-centered data.

Nevertheless, research institutions and other organizations are increasingly taking interest and funding patient-centered research. The National Institutes of Health (NIH) has 30 active Funding Opportunity Announcements (FOA) related to SDM as well as 58 active FOAs related to patient outcomes.<sup>45</sup> PCORI also continues to offer grants and support funding of patient-centered research efforts. The growing interest and funding behind patient-centered data collection raises many future opportunities to advance the infrastructure of patient-centered research.

In the absence of mutually accepted data standards (i.e. standardized file formats, data structures, variables, and definitions), stakeholders spanning the healthcare spectrum are beginning to identify and address ways in which organizations can create and improve methodological standards for RWD collection and to determine clinically relevant differences and statistical significance of the evidence generated. In 2017, the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) and the International Society for Pharmacoepidemiology (ISPE) created a task force and published “Good Practices for Real-World Data Studies of Treatment and/or Comparative Effectiveness” intended to help researchers engage in good procedural practices for RWD collection and use.<sup>46</sup> The Good ReseArch for Comparative Effectiveness (GRACE) Initiative published a validated checklist and other guidance, providing good practice principles for observational studies.<sup>47</sup> Most recently, in

---

<sup>41</sup> U.S. Food and Drug Administration. “Framework for FDA’s Real-World Evidence Program.” December 2018.

<sup>42</sup> Ibid.

<sup>43</sup> Morton, Sally C. et al. “Standards and Guidelines for Observational Studies: Quality Is in the Eye of the Beholder.” *Journal of Clinical Epidemiology*. March 2016. 71: 3-10.

<sup>44</sup> Ibid.

<sup>45</sup> National Institutes of Health. NIH Guide to Grants and Contracts. Accessed March 2019.

<sup>46</sup> Berger ML, Sox H, Willke R.J. Good Practices for Real-World Data Studies of Treatment and/or Comparative Effectiveness: Recommendations from the Joint ISPOR - ISPE Special Task Force on Real-World Evidence in Health Care Decision Making. *Value Health*. 2017; (8): 1003-1008.

<sup>47</sup> Good ReseArch for Comparative Effectiveness. Available at: <https://www.graceprinciples.org/>.

December 2018, the FDA published its Framework for Real-World Evidence, intended to promote consistency and quality of RWE collection and use.<sup>48</sup> These initiatives, as well as other efforts, underscore the need to standardize such collection and use of RWD.

**Recommendation 1: Implement a patient-centered process for formulating a common data architecture to improve the usability of RWD.**

As previously described, professional societies, research organizations, regulatory bodies, and many other groups are taking interest and acknowledging the benefit of RWD. Accordingly, these entities also recognize the need for improved standardization of these data. Many organizations have published standards or guidance to assist the creation of a governed RWD infrastructure, however, there are few mutually agreed upon architectural RWD guidances.

Recognizing these discrepancies, Avalere has outlined 4 steps that can assist the longer-term aggregation and use of methodologically rigorous RWD.

- **Collaborate with patients and/or patient representatives to ensure that a common data architecture comprehensively reflects patients' values** – To assure that the distinct values patients consider and matter the most in their care journey are captured in a standardized data structure, research entities can collaborate and integrate these patient values into data collection guidance or standardization efforts. Patient perspectives vary based on each individual patient or among different patient populations.
- **Invest in the consistent use of validated data collection instruments** - Many researchers are concerned with bias or confounding factors in studies that produce RWD. Additionally, not every data collection sponsor reports use of, or even uses of, a validated instrument to aggregate patient-centered data. To produce methodologically rigorous results, researchers can identify and regularly utilize validated instruments to elicit patient-centered data.\* Such validated instruments include those that measure QoL, such as SF-36 or PROMIS-29, and others that measure different patient-centered outcomes (e.g., complexity of regimen, medical costs).
- **Monitor relevant processes/structures related to data standardization to support ongoing collection of patient-centered outcomes within RWD** – Research organizations, regulatory institutions and other stakeholders continue to provide guidance that begins to standardize the collection of RWD of patient-centered outcomes. This is exemplified through ISPOR/ISPE “Good Practices for Real-World Data Studies of Treatment and/or Comparative Effectiveness”, the FDA’s RWE Framework for Real-World Evidence, and other initiatives. Although distinct, these guidances support longitudinal collection of RWD by providing researchers with foundational steps necessary to collect such data rigorously. Moreover, the FDA has noted the value of

---

<sup>48</sup> Food and Drug Administration. “Framework for FDA’s Real-World Evidence Program.” December 2018.

PRO use from initial clinical trial implementation to post marketing surveillance, which can provide more consistency in data collection and evaluation for regulatory bodies.<sup>49</sup>

- **Identify and utilize components of a technical infrastructure that can support ongoing aggregation of RWD** – The use of data collection platforms and other health information technology (HIT) applications, such as electronic health records (EHRs) and clinical decision support systems (CDSS), can help to aggregate patient-centered RWD that can be leveraged to generate RWE. HIT tools can also support a more structured data collection and practical application. The growth of interoperability, as illustrated by initiatives such as The Fast Healthcare Interoperability Resource (FHIR), can also serve as a technical vehicle to support ongoing collection of RWD. By identifying other appropriate platforms, such as those referenced in Diagram 3, and promoting their use, especially those that map to the PPVF’s domains, criteria and measures, researchers and providers will be aware of, and begin to leverage, these structures that can support the generation of a common data architecture for patient-centered RWE collection.

It is important to consider how the aforementioned steps may be shaped by a specific therapeutic area. Certain conditions, such as advanced breast cancer, may be more symptomatic than others like heart disease. As such, researchers should be cognizant of how different symptoms may be presented by condition and accordingly, be aware of the appropriate ways to monitor and evaluate these symptoms and their effects on the patient experience.

As the patient-centered data system continues to evolve and regulatory bodies and other institutions begin to publish additional guidance for its standardized collection, the specifics of the proposed steps may be altered to best reflect the state of RWD collection. Nonetheless, the underlying goal of each step will remain: assist the generation of a common data infrastructure for RWD.

### **Recommendation 2: Advance incentives and structural changes to encourage researchers to routinely include patient-centered outcomes in study design.**

The use of patient-centered data can empower patients to choose treatments that are appropriate and personally relevant. However, research institutions, professional societies, and other stakeholders may face many barriers in collecting these data. Some researchers and organizations are concerned with the potential bias and impact of confounding factors in observational studies.<sup>50</sup> Others point to the aforementioned issue of minimal data standardization and governance.<sup>51</sup> A key challenge many value assessment and other research organizations encounter is the lack of availability of patient-centered data. As such, there exists an opportunity to design, promote, and employ incentives aimed at increasing the routine collection of patient-centered RWD.

---

<sup>49</sup> Center for Devices and Radiological Health, U.S. Food and Drug Administration. Value and Use of Patient Reported Outcomes (PROs) in Assessing Effects of Medical Devices, CDRH Strategic Priorities 2016-2017.

<sup>50</sup> Garrison, Louis P. “Using Real-World Data for Coverage and Payment Decisions: The ISPOR Real-World Data Task Force Report.” *Value in Health*. 2007. 10 (5): 326-335.

<sup>51</sup> Ibid.

Below, Avalere has identified 2 potential directions that can help to increase the availability and support the routine collection of patient-centered data.

- 1. Incorporate patient-centered outcomes as an endpoint in outcomes-based contracting:** Payers and manufacturers have shown increasing interest and participation in value-based arrangements as a potential way to save costs and provide quality care to patients. A 2017 survey of health plans found that 70% of health plans reported favorable attitudes towards outcomes-based contracting (OBC).<sup>52</sup> Moreover, 25% of respondents reported having at least 1 OBC in place and an additional 30% reporting negotiation for 1 or more.<sup>53</sup> With this growing interest and engagement in OBCs, an opportunity exists to use patient-centered outcomes as an endpoint, ultimately contributing to more routine collection of these data. Embedding patient-centered outcomes into contract design would in turn increase data availability, as parties involved in such contracts would need to collect those data in order to evaluate performance. As total costs of care continue to rise, especially for chronic conditions, the integration of patient-centered outcomes in OBCs can help payers, providers, and patients themselves track not only their needs and preferences, but also their adherence, effectiveness, and overall utilization.
- 2. Monitor and prepare for increased guidance from FDA regarding methodology and use for RWD:** The FDA continues to show interest and commitment to providing guidance for the methodologically rigorous collection and appropriate use of RWD. In August 2017, the FDA published “Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices” shortly followed by the release of the RWE Framework in December 2018. The FDA also announced the launch of a new digital tool to help collect real-world data from patients, intended to help inform regulatory decision-making. These actions suggest the FDA’s awareness of RWD’s significance and their thought process behind how to best collect and integrate RWD into regulatory decision-making. Accordingly, since the majority of stakeholders turn to the FDA for data-related guidance, research entities could benefit from the preparation and initial collection of RWD to best position themselves for the most appropriate aggregation and utilization of RWD, as preliminary outlined by the FDA, in the long-term.

As organizations begin to explore the above avenues in which research institutions and other entities can begin to routinely collect RWD, organizations may benefit from identifying a specific type of RWD to use and initially learn from to set the path for long-term, rigorous data collection. Demonstrated in Focus Area 1 of the short-term recommendations, patients value the consideration of quality of life (QoL) in treatment decision-making. Additionally, there is an existing foundation for the collection and use of QoL data as illustrated in Avalere’s preliminary assessment of RWD. Hence, QoL can serve as a starting point for pursuance of the outlined directions, providing initial learnings to build a larger patient-centered data infrastructure for RWD.

---

<sup>52</sup> “Health Plans Are Actively Exploring Outcomes-Based Contracts.” Avalere Health. May 30, 2017.

<sup>53</sup> Ibid.

### **Recommendation 3: Implement policy changes that encourage providers to routinely assess QoL and other patient-centered outcomes through existing programs.**

Clinicians are well positioned to regularly report patient-centered outcomes, especially those involved in policy programs that mandate such data collection for payment determination and overall program evaluation. These programs include the Merit-Based Incentive Payment System (MIPS), the Oncology Care Model (OCM), alternative payment models (APMs) and other Centers for Medicare & Medicaid Innovation (CMMI) demonstrations. Within some of these programs, the infrastructure already exists to readily collect these data. Hence, there is an opportunity to encourage providers to leverage these existing platforms and requirements to routinely collect and assess QoL and other patient-centered outcomes. Below, Avalere has outlined 3 policy levers that can be utilized to promote this collection.

- **Clinical Practice Improvement Activities (CPIAs) under MIPS** – Since its introduction in 2015, individual clinicians and provider groups are increasingly participating in the Merit-Based Incentive Payment System (MIPS). MIPS performance evaluation is based on 4 scoring elements: quality, advancing care information, cost, and clinical practice improvement activities. Specifically, CPIAs can be leveraged to promote the routine collection of patient-centered outcomes. With CPIAs, eligible groups or individual providers choose the improvement activities that best fit their practice. Once chosen, clinicians must report on their attainment against the selected improvement activities in order for CMS to determine the provider’s overall MIPS score. Many of the CIA categories and qualifying activities seek to improve patient engagement and map to the PPVF domains and criteria. To that end, CPIAs and their associated reporting requirements can be used to promote the collection of patient-centered data.
- **Quality Measures under OCM** – OCM, a CMMI demonstration running from 2016-2021, is a payment and delivery model intended to decrease the cost and improve the quality of oncology care.<sup>54</sup> Participating clinicians must report on certain quality measures, some of which map to the PPVF, in order to determine performance that influences provider reimbursement for care. The OCM also encourages the use of shared decision-making (SDM) to help patients document their care plan in accordance to the 13 components of the Institute of Medicine’s Care Management Plan.<sup>55</sup> Finally, future areas within the Consensus Core Set: Medical Oncology Measures, a reporting option for OCM-participating clinicians, include outcomes that align to PPVF domains and criteria, such as patient & family costs, QoL, and efficacy & effectiveness.<sup>56</sup> Hence, this mandatory reporting can be used as a vehicle to increase the availability of patient-centered data.
- **Accountable Care Organizations (ACOs) in the Medicare Shared Savings Program (MSSP)** – The MSSP encourages groups of providers, other care team members, and health systems to voluntarily form an ACO and provide coordinated, high-quality care to

<sup>54</sup> Centers for Medicare & Medicaid Services. Oncology Care Model. April 2019.

<sup>55</sup> Centers for Medicare & Medicaid Services. Oncology Care Model Overview. February 2019.

<sup>56</sup> Centers for Medicare & Medicaid Services. Consensus Core Set: Medical Oncology Measures. Version 1.0. November 2015.



patients. MSSP requires participants to submit quality measure data that span 4 key domains in order to assess performance. In particular, the reporting of measures within the patient/caregiver experience domain can serve as a vehicle to collect patient-centered data that aligns to PPVF criteria, such as goals/expectations and QoL.<sup>57</sup> As such, the reporting of these data can contribute to increasing the overall breadth of patient-centered data.

The 3 outlined programs can serve as existing policy levers to improve the availability of patient-centered data. Moreover, as CMS continues to identify ways to provide value-based care to beneficiaries through CMMI demonstrations, other policy programs may be leveraged in the future to contribute to the routine collection of such data.

---

<sup>57</sup> Centers for Medicare & Medicaid Services. Medicare Shared Savings Program – Quality Measurement Methodology and Resources. February 2019.

## Focus Area 2: Evolution of FDA Requirements

### Background: FDA Patient-Centered Initiatives

Stakeholders spanning the healthcare spectrum continue to advance appropriate collection and use of patient-centered data, including RWD. In particular, the FDA has engendered and progressed initiatives to help guide broad-based, rigorous aggregation and utilization of patient-centered data. For instance, established under the Prescription Drug User Fee Act V (PDUFA V), the FDA's Center for Drug Evaluation and Research (CDER) launched the Patient-Focused Drug Development (PFDD) as an approach to help ensure the meaningful description and inclusion of patients' experiences, perspectives, needs and priorities into drug development and evaluation.<sup>58</sup> Additionally, to help encourage and inform medical device sponsors' appropriate use of patient-reported outcomes (PROs), the FDA's Center for Devices and Radiological Health (CDRH) published a PRO compendium, which enumerates selected PROs that regularly appear on device labels based on recent approvals and classifications.<sup>59</sup> Most recently, the FDA released its Framework for RWE Program, which outlines a multifaceted approach to evaluating RWE in the context of regulatory decision-making.

Given that the FDA's influence in shaping research on emerging therapies, the evolution of FDA requirements to allow for or mandate the inclusion of standardized patient-centered data, such as RWD can help to shape the larger patient-centered data architecture.

### Recommendation 1: Create regulatory structures that incentivize researchers to include QoL in clinical trial design.

The inclusion of QoL as an endpoint into clinical trial design can help to incorporate the patient perspective into regulatory decision-making and expand the availability of patient-centered data.

Avalere has identified 4 ways in which the FDA can either create new regulatory structures or alter existing workstreams to incentivize researchers to incorporate QoL into clinical trial design:

1. **Encourage incorporation of QoL into clinical trial design in updates to guidance documents:** FDA's incorporation of QoL into expectations for drug development processes through updates to various guidance documents can re-focus researchers on how to best collect QoL-related data from the beginning to end of drug development. Guidance documents fall into many categories, including generics, biosimilars, RWD/RWE use and more. In particular, the FDA's current update to its draft guidance on rare diseases serves as an immediate opportunity for QoL incorporation. Currently, the FDA is in the process of revising draft guidance on developing treatments for rare diseases.<sup>60</sup> As part of this process, the FDA is soliciting feedback from patients and caregivers on the impacts of rare diseases on patients' QoL, suggesting an opportunity to include QoL as an endpoint for clinical trial design in the final guidance document.

<sup>58</sup> U. S. Food and Drug Administration. "CDER Patient-Focused Drug Development." December 20, 2018.

<sup>59</sup> U. S. Food and Drug Administration. "Value and Use of Patient-Reported Outcomes (PROs) in Assessing Effects of Medical Devices." *CDRH Strategic Priorities 2016-2017*. 2016.

<sup>60</sup> Food and Drug Administration. "Rare Diseases: Common Issues in Drug Development Guidance for Industry." February 2019.

Moving forward, the inclusion of QoL into the current draft guidance for rare diseases may help to inform the incorporation of QoL into other future updates or draft regulatory guidance. As researchers, especially those seeking drug or device approval, look to the FDA for clinical trial design guidance, there exists an opportunity to regularly incorporate QoL into these guidances, incentivizing increased collection of QoL data.

2. **Embed QoL into benefit-risk assessments for premarket approval:** An opportunity exists to integrate QoL into the evolving regulatory infrastructure by shaping the data considered in benefit-risk assessments for premarket approval of pharmaceutical products and medical devices. More specifically, researchers have begun to assess how patient preferences may be incorporated into regulatory assessments. A 2015 study assessing the tradeoffs among effectiveness, safety, and other traits of weight-loss devices found that patient preferences could be used to make regulatory decisions more patient-centered.<sup>61</sup> Researchers also concluded that the methodology to elicit and evaluate patients' tradeoffs could be applicable to other medical products.<sup>62</sup> By incorporating QoL into benefit-risk assessments for premarket approval, researchers may be more inclined to include QoL into clinical trial design, ultimately expanding the breadth of QoL-related data.
3. **Promote use of QoL as a surrogate or intermediate clinical endpoint in the FDA's Accelerated Approval pathway:** Since its legislative introduction in 2012, the Accelerated Approval pathway has been used to approve drugs that treat serious conditions and fill an unmet clinical need. When pursuing the Accelerated Approval pathway, researchers must utilize surrogate or intermediate clinical endpoints to support the proposed clinical benefit of the product. For accelerated approvals, clinical benefit is defined as "a positive therapeutic effect that is clinically meaningful in the context of a given disease."<sup>63</sup> Many researchers use more traditional clinical endpoints, such as progression free survival or disease-free survival to suggest clinical benefit under an accelerated approval.<sup>64</sup> Nevertheless, QoL can be used as a surrogate or intermediate clinical endpoint to support the proposed clinical benefit of a product since it can be used to measure a therapeutic effect of a product. In response, the collection of such QoL data for accelerated approval can help to increase the availability of patient-centered data.
4. **Leverage existing PRO compendium for medical devices to formulate best practices for PRO measurement for drugs** – Research organizations regularly incorporate certain endpoints, such as survival or tumor response, into clinical trial design. With this more routine use of traditional clinical outcomes, research entities are more familiar with the different measurements to assess these endpoints (e.g., overall survival, progression-free survival, etc.). However, researchers have less understanding

---

<sup>61</sup> Ho, Martin P, et al. "Incorporating Patient-Preference Evidence into Regulatory Decision Making." *Surgical Endoscopy*. October 2015. DOI: 10.1007/s00464-014-4044-2

<sup>62</sup> Ibid.

<sup>63</sup> U. S. Food & Drug Administration. Accelerated Approval. January 2018.

<sup>64</sup> U. S. Food & Drug Administration. Table of Surrogate Endpoints That Were the Basis of Drug Approval or Licensure. Updated March 2019.

of what types of patient-centered outcomes are available and how to measure these endpoints in clinical trials, resulting in less use of them. The publication of guidance, such as the existing PRO compendium for medical devices, can help researchers properly embed and evaluate patient-centered outcomes into clinical trial design. The PRO compendium for medical devices outlines selected PROs and their associated measurement tools that have appeared in device labels based on recent approvals and classifications.<sup>65</sup> Many of these PROs map to the PPVF, in particular QoL. A similar guidance document for drugs can guide researchers into appropriate use of patient-centered outcomes and measurement instruments.

The 4 aforementioned channels to more routinely include QoL in clinical trial design can help the FDA advance their exploration and generation of ways to better integrate the patient voice into regulatory guidance and decision-making. Moreover, incentivizing the collection of QoL can provide learnings for the integration of other patient-centered outcomes, such as complexity of regimen or patient preferences, that align to the PPVF's domains, criteria, and measures.

**Recommendation 2: Advance the use of RWE for regulatory decision-making via the newly created RWE Framework.**

To date, there has been substantial interest, but limited use of RWE to support regulatory decisions. Nonetheless, the FDA recognizes the value that RWE can offer in regulatory decisions regarding the effectiveness of drug products and recently created their Framework for the Real-World Evidence Program. Three key considerations guide the Framework.<sup>66</sup>

1. Whether the RWD sources are fit for analysis
2. Whether the trial or study design used to generate RWE can provide adequate scientific evidence to answer or help answer the regulatory questions
3. Whether the study conduct meets FDA regulatory requirements (e.g., for study monitoring and data collection)

The newly created RWE Framework provides an opportunity to promote and advance the collection and utilization of methodologically rigorous RWE for regulatory decision-making. Four key program ideas are most relevant to advancing the use of RWE.

- **FDA will review and, where applicable, publish guidance on potential gaps in RWD sources and strategies to address them** – Electronic health records (EHRs) and medical claims data continue to aggregate electronic patient data. However, much of these data remain siloed due to interoperability challenges. As stakeholders gradually address these barriers, the use of EHRs and other electronic data collection platforms can help to increase the availability of patient-centered data by providing an infrastructure to rapidly collect and assess data. The FDA's identification of current gaps within RWD sources and publication of guidance on how to address such challenges can

<sup>65</sup> U. S. Food & Drug Administration. CDRH Patient-Reported Outcomes (PRO) Compendium.

<sup>66</sup> U. S. Food and Drug Administration. "Framework for FDA's Real-World Evidence Program." December 2018

help to streamline the development of a standardized structure for the routine collection of patient-centered data within a diversity of RWD sources.

- **FDA’s RWE Program will develop guidance on considerations for designing clinical trials that include pragmatic design elements and that generate evidence of effectiveness for regulatory decisions** – The FDA notes the strength of both RCTs and RWE and continues to identify ways to create hybrid trials including traditional and pragmatic clinical trial elements. As presented in Focus 2 of the short-term recommendations, opportunities exist to balance RWE and RCTs to more holistically capture the patient experience. Hence, FDA’s additional guidance on specific ways to consider and use both in data collection and regulatory decision making can help to spark growth in rigorously collected patient-centered data, such as RWD.
- **Adapting and building on the Pharmacoepidemiologic Guidance, FDA plans to issue guidance about observational study designs using RWD, including whether and how these studies might provide RWE to support product effectiveness in regulatory decision making** – Further guidance on how observational study designs can be formulated to best collect RWD rigorously can help to guide and promote a more routine collection of standardized and rigorous RWD. Currently, a lack of transparency regarding study results has sparked concerns from regulatory agencies and other entities utilizing RWD. Additional transparency via required reporting of certain summary trial results can limit these concerns.
- **FDA will assess the data standards and implementation strategies required to use RWD/RWE at FDA, identify any gaps between those requirements and existing FDA systems, and recommend a path forward to ensure that RWD/RWE solutions are an integral part of the full drug development and regulatory life cycle at FDA** – In listing activities to support the use of RWE in regulatory decision making, the FDA acknowledges the value that RWE can offer in the drug development and approval process. This continued assessment of data standards and strategies can direct research organizations to more routinely and rigorously collect data that are compatible to existing regulatory workstreams. Moreover, such guidance can help to assure researchers that they are collecting RWD that is relevant and consistent with regulatory standards.

## Focus Area 3: Increased Availability of Patient-Centered Data

### Background:

Although regulatory bodies and research institutions have started to promote initiatives that aim to advance the collection of patient-centered data (e.g., FDA’s PFDD),<sup>67,68,69</sup> these data are not routinely collected in a standardized fashion.<sup>30</sup> As such, there exists a data availability gap in several of the key outcomes that matter most to patients and caregivers in making healthcare decisions. In particular, data that align to the PPVF’s Patient Preferences and Patient & Family Costs domains are limited, despite research that indicates their importance in patients’ decision making.<sup>70,71</sup>

This data availability gap in patient-centered data presents broader challenges, as the lack of data may limit the extent to which patient-centered outcomes can be used to influence regulatory workstreams and payer coverage and reimbursement decisions. A more deliberate approach to the current collection and management of patient-centered data would facilitate important advances in patient-centered value assessment, specifically those related to patient & family cost, complexity of regimen, and patient preferences.

**Recommendation 1: Encourage payers and other institutions to identify and use structures to appropriately aggregate and incorporate patient out-of-pocket (OOP) costs in value assessment calculations.**

Avalere’s preliminary landscape assessment around cost data identified very few sources for data on patients’ direct medical costs. This gap in the availability of patient OOP cost data represents an opportunity to encourage payers and other institutions to increase the availability of OOP medical cost data. Payers are well positioned to collect these data, since they already have patient-centered medical data available to administer claims and benefits. Moreover, through routine monitoring and evaluation of patient adherence to products, payers have the ability to collect and assess costs related to device maintenance and routine patient OOP costs, both of which align to PPVF measures. Finally, improved transparency around costs of care has the potential to improve patients’ adherence to their treatment plans.<sup>72</sup> Long-term poor patient adherence can negatively affect system utilization and influence the amount that payers and similar institutions contribute to patients’ care costs. To that end, improved collection and evaluation of patient OOP costs data by payers can offer potential cost savings for these institutions.

---

<sup>67</sup> U.S. Food and Drug Administration. “CDER Patient-Focused Drug Development.”

<sup>68</sup> Berger ML, Sox H, Willke RJ. “Good Practices for Real-World Data Studies of Treatment and/or Comparative Effectiveness: Recommendations from the Joint ISPOR – ISPE Special Task Force on Real-World Evidence in Health Care Decision Making.”

<sup>69</sup> Good Research for Comparative Effectiveness. Available at: <https://www.graceprinciples.org/>.

<sup>70</sup> CancerCare. “CancerCare Patient Access & Engagement Report.” New York: CancerCare; 2016.

<sup>71</sup> Buzaglo J.S., Miller, M.F., Longacre, M.L. “Cancer Patients’ Priorities When Considering a Treatment Decision.” Poster presented at 8th Biennial Cancer Survivorship Research Conference: Innovation in a Rapidly Changing Landscape.

<sup>72</sup> Centers for Disease Control and Prevention. “QuickStats: Percentage of Persons of All Ages Who Delayed or Did Not Receive Medical Care During the Preceding Year Because of Cost, by U.S. Census Region of Residence — National Health Interview Survey, 2015. MMWR Morb Mortal Wkly Rep 2017;66:121. DOI: <http://dx.doi.org/10.15585/mmwr.mm6604a9External>

Given these existing capabilities and resources to collect patient medical costs data, payers and similar institutions can advance the collection of such data not only for their purposes, but also to use in value assessments to generate a more personally relevant calculation to patients. As such, there are more specific ways in which payers can aggregate patient direct medical costs in a more standardized fashion. For instance, payers can begin to identify technical structures that best support the consolidation of patient costs from the various care team members. Currently, there is little coordination or transparency regarding patient cost among the different members of the patient's care team. However, each care team member does code and submit the appropriate claims for a given treatment to a patient's respective health plan. Accordingly, payers can begin to identify the infrastructural elements that can support routine aggregation and analysis of patient OOP costs data. In particular, the systems used in vertically integrated health systems can provide learnings for how to best collect and assess coordinated patient OOP cost data.

Additionally, payers can better collaborate with providers, wholesale distributors, and other parties operating across the supply chain and the patient's care journey in order to consolidate and normalize the typical patient OOP cost for a given treatment. The use of rebates and other innovative pricing structures, like indication-based pricing, as well as lack of coordination among these stakeholders make the establishment of a typical patient OOP cost more difficult. Hence, increased partnership and transparency among these stakeholders can illuminate individual patients' true OOP treatment costs.

### **Recommendation 2: Promote payer understanding and collection of non-medical cost data.**

As outlined in the previous recommendation, payers are well positioned to collect patient direct medical data. However, there is even less availability of non-medical costs to the patients and their families. Although these data are not routinely collected in the current patient-centered data landscape, payers have an opportunity to better understand and collect such data to help inform their workstreams as well as to be used in value assessments. The following points are advantages to payers' collection of patient indirect costs.

- Collecting non-medical cost data would allow payers to track the true cost of the treatments on patients and use those data to develop and implement programs to reduce financial burden for patients.
- Payers and providers alike would benefit from seeing increased adherence to treatment regimens from their patients.
- The estimation of indirect costs of care can help payers prioritize interventions to overcome the cost barriers of treatment. Plans could use these data to estimate the impact of indirect costs of care on member populations by running data analytics programs to identify trends in patient behavior in relation to treatment outcomes from these data.

Despite the emergence of sources and methods to collect patient direct/OOP cost data, methods to understand and aggregate data on non-medical medical costs are in their infancy. Thus, to collect indirect medical cost data, payers and other institutions can begin to leverage existing workflows like those outlined in the previous recommendation, as well as deploy their own methods. For instance, 1 study researched the limited data available regarding the cost of care (CoC) in patients with androgen independent prostate carcinoma (AIPC) and the lack of data on the impact of direct non-medical and indirect costs. Researchers collected direct medical cost data using a developed questionnaire titled “the Collection of Indirect and Nonmedical Direct Costs” (COIN) form.<sup>73</sup> Patients filled out a baseline economic assessment form that requested demographic and income data. Researchers extracted data from those surveys, including employment status, occupation, earnings, and medical insurance data, and used the mean of each group for the data analysis that determined the CoC for that patient population group. This study illustrates how payers and other institutions can consider and begin to implement similar methods to determine indirect medical costs of care for certain patient populations.

Additionally, collecting patient indirect costs data may be more complex because the associated measures are more difficult to quantify. As such, payers may need to generate and employ an imputation process to quantify and analyze these non-medical cost data. Sage Research Methods defines imputation as “a statistical process that statisticians, survey researchers, and other scientists use to replace data that are missing from a data set... to improve the accuracy of their data sets.”<sup>74</sup> For example, some patient registries and other RWD sources collect data on the non-medical costs, such as administrative burden of specific treatments, the burden of travel, or costs of supportive care. Payers may then be able to link those data to typical direct costs of these services to estimate these non-medical and future costs of care.

### **Recommendation 3: Incorporate tools at point of care that begin to capture patient/family medical and non-medical costs.**

Considering the lack of patient-centered cost data currently available, incorporating point-of-care tools to document and facilitate conversations around costs may help generate these data and fill in these gaps. Point-of-care tools can help providers discuss the various dimensions of costs of care; in the process, there may be an opportunity to generate RWD. Additionally, incorporating such tools can also encourage clinicians to document and consider CoC discussions when helping their patients make treatment decisions. Avalere has identified 3 types of tools that can be incorporated at the point of care to capture patient/family non-medical and medical cost data.

1. **Screening tool for cost burden:** Screening tools for cost burdens, such as infographics or discussion guides<sup>75</sup>, help structure conversations between patients and clinicians and allow for subsequent documentation of costs burdens. Using screening tools can help

<sup>73</sup> Sherman, Eric, et. al. “The Collection of Indirect and Nonmedical Direct Costs (COIN) Form, A New Tool For Collecting the Invisible Costs of Androgen Independent Prostate Carcinoma”. *Cancer*. February 2001.

<sup>74</sup> Lavrakas, P. J. (2008). *Encyclopedia of survey research methods* Thousand Oaks, CA: Sage Publications, Inc. doi: 10.4135/9781412963947

<sup>75</sup> Avalere Health, Essential Hospitals, et. al. “Structuring the Conversation: How to Talk to Your Patients About the Costs of Their Care, Cost-of-Care Conversations Practice Brief #4”. November 2018.

providers capture medical and non-medical cost burdens reported by patients during point of care.<sup>76</sup> One example of a point of care tool is Dartmouth's collaboRATE, which contains 3 questions that patients or their representatives complete following a clinical encounter. Together, the responses can inform future conversations between patients and clinicians, while also collecting important financial toxicity data.

2. **Cost Transparency Tools:** Cost Transparency Tools inform both patients and clinicians about cost considerations by calculating and displaying all the costs that go into treatment, both direct and indirect. These tools can help initiate CoC conversations between patients and clinicians.<sup>77</sup> In 1 example, Sinai Urban Health Institute and the University of Illinois at Chicago developed a chart that showed a breakdown of approximate indirect costs for high-risk pregnancy appointments, including travel time, cost of transportation, and other factors such as food and parking.<sup>78</sup>
3. **Tools to document clinician-reported cost burden in EHRs:** Once patient data is generated at the point of care, tools that document these data become important to capturing and recording that data. One strategy is to use tools that document these data into EHRs. Using tools or implementing a mechanism to capture cost concerns, strategies used to address those concerns, and other relevant data points can be useful information that the patient's care team and other clinicians can have access to in the patient's record.<sup>79</sup> Moreover, documentation tools for EHRs could be readily incorporated into the clinical workflow, as clinicians could directly enter cost data generated during point of care.

While the incorporation of these tools can catalyze the collection of non-medical and medical costs data, clinicians should also be aware of how they can be integrated into existing workstream with minimal disruption. Several best practices exist for creating a workflow and establishing systems to discuss and properly document CoC conversations in order to collect cost-related data:

- Employ a team-based approach and clearly outline roles
- Establish a process for identifying and documenting patient cost concerns
- Implement measures to track CoC conversations
- Ensure CoC workflow is integrated into existing processes

---

<sup>76</sup> Av alere Health, Essential Hospitals, et. al. "Structuring the Conversation: How to Talk to Your Patients About the Costs of Their Care, Drug Cost Pocket Card". November 2018.

<sup>77</sup> Av alere Health, Essential Hospitals, et. al. "Structuring the Conversation: How to Talk to Your Patients About the Costs of Their Care, Cost-of-Care Conversations Practice Brief #2". November 2018.

<sup>78</sup> Av alere Health, Essential Hospitals, et. al. "Structuring the Conversation: How to Talk to Your Patients About the Costs of Their Care, Cost-of-Care Conversations Practice Brief #5". November 2018.

<sup>79</sup> Ibid.

#### Recommendation 4: Leverage tools and resources to bolster the collection of complexity of regimen data through clinical trials.

Currently, complexity of regimen data are not being widely or systematically collected.<sup>80</sup> Regimen complexity has been associated with nonadherence, hospital readmission, and adverse drug events.<sup>81,82,83</sup> Complexity of regimen data include taking into account the patient's lived experience, as well as understanding the path of treatment from the patient's perspective (for example, number of times per week a patient needs to travel to a clinic for an IV administration). In addition, studies have shown a link between reduction of complexity of regimen and an increase in patient adherence to treatment regimens, which in turn can result in more health benefits for patients.<sup>84,85</sup> Incorporating collection and discussion of these data into clinical trials and at the point of care can help to fill those gaps.

One example of the importance of leveraging tools to bolster collection of complexity of regimen data is the PrefMab study. As explicated in Focus Area 3 of the short-term recommendations, the PrefMab study compared patient preferences for Rituxan Hycela (subcutaneous-SC) and Rituxan (intravenous-IV).<sup>86</sup> Using the Rituximab Administration Satisfaction Questionnaire (RASQ), researchers found that the majority of patients (77%) preferred Rituxan Hycela (SC) over Rituxan (IV), pointing to less time in the clinic and more comfort during administration as key rationale for their preference.<sup>87</sup> Notably, sponsors of Rituximab Hycela engendered and validated the RASQ to assess patient perceptions and satisfaction with Rituximab SC or IV. Specifically, questionnaire concepts fell into 2 categories: treatment satisfaction and impact of treatment administration.

The PrefMab study not only exemplifies how the use of patient-centered data can be used to support regulatory processes, but also illustrates how the use of a validated instrument can encourage the collection of complexity of regimen data in a methodologically rigorous way. Thus, there lies an opportunity to use the PrefMab study as a roadmap on how to identify, validate and utilize other resources to bolster the collection of regimen data.

---

<sup>80</sup> Wimmer, Barbara C., et al. "Medication Regimen Complexity and Polypharmacy as Factors Associated With All-Cause Mortality in Older People: A Population-Based Cohort Study." February 2016. *Annals of Pharmacotherapy*; 50(2),89-95. doi:10.1177/1060028015621071.

<sup>81</sup> Dierich MT, Mueller C, Westra BL. Medication Regimens in Older Home Care Patients. *Journal of Gerontological Nursing*. 2011. 37,45-55. doi:10.3928/00989134-20111103-02.

<sup>82</sup> Willson MN, Greer CL, Weeks DL. Medication Regimen Complexity and Hospital Readmission for an Adverse Drug Event. *Annals of Pharmacotherapy*. November 2013. 48:26-32. doi:10.1177/1060028013510898.

<sup>83</sup> de Vries ST, Keers JC, Visser R, . Medication Beliefs, Treatment Complexity, and Non-adherence to Different Drug Classes in Patients with Type 2 Diabetes. *Journal of Psychosomatic Research*. 2014. 76(2),134-138. doi:10.1016/j.jpsychores.2013.11.003.

<sup>84</sup> Ingersoll KS, Cohen J. The Impact of Medication Regimen Factors on Adherence to Chronic Treatment: A Review of Literature. *Journal of Behavioral Medicine*. June 2008. 31(3), 213-224. doi: 10.1007/s10865-007-9147-y.

<sup>85</sup> Corsonello A, Pedone C, Lattanzio F, et al. Regimen Complexity and Medication Nonadherence in Elderly Patients. *Therapeutics and Clinical Risk Management*. 2009. 5, 209-216.

<sup>86</sup> Hoffmann-La Roche. "A Study of Participant Preference with Subcutaneous Versus Intravenous MabThera/Rituxan in Participants with CD20+ Diffuse Large B-Cell Lymphoma or CD20+ Follicular Non-Hodgkin's Lymphoma Grades 1, 2 or 3a." National Institutes of Health, U.S. National Library of Medicine. 2018

<sup>87</sup> Ibid.

## Recommendation 5: Promote collection of methodologically rigorous data to inform individual-level patient preferences and decision making.

Timely provision of patient preference data to individual patients can help patients make more informed healthcare decisions that better reflect their personal preferences. Recent studies have shown that patient care improves when individual patients' needs and preferences are taken into account. In 1 study, researchers used a patient healthcare preference questionnaire to determine whether incorporating individual patient preferences led to improved quality of care. This study showed that incorporating patient's needs and preferences, led to improved quality of care for patients.<sup>88</sup> A report by *CancerCare* also found that many patients wished that they were being taken care of holistically, including having more information to be more engaged at the point of treatment decision making.<sup>89</sup>

Despite the value that individual patients may place on integrating their preferences into decision making, there is currently a lack of standardized collection of these data. Accordingly, Avalere has defined 3 channels that support the methodologically rigorous collection of patient-centered data at the point of treatment decision-making for providers.

1. **Utilize or invest in the validation of tools that can collect these data:** SDM tools that discuss costs would be especially valuable here, given the current lack of data surrounding medical/non-medical cost data. These data could also be collected via forms that patients would fill out prior to their visit.
2. **Integrate use of accountability tools during treatment decision-making:** Using accountability tools to ensure that patient preference data are generated and captured can increase the overall availability of patient-centered data available.
3. **Identify and leverage platforms that are capable of collecting these data:** Once these data are collected from patients, identifying and leveraging EHRs and other health IT platforms can be used to structure, manage, and integrate data into clinical workflows. Organizing data in systems such as patient registries could also increase availability of data and allow providers and researchers to track it over time and use it to inform conversations with individual patients.

## Recommendation 6: Support advancement of methodologically rigorous data on population-level patient preferences.

The aggregation and use of population-level patient preferences data can also help inform patients' healthcare decision making and various regulatory processes, such as product approval or guidance document development. Nevertheless, the scope of population-level patient preferences data collection is limited. In Avalere's preliminary assessment of RWD sources, only 10 of 43 sources reported collection of patient preference data that mapped to the PPVF Patient Preferences domain. This disconnect between the advantages of

<sup>88</sup> Wessel, et. al. "Gender-Related Needs and Preferences in Cancer Care Indicate the Need for an Individualized Approach to Cancer Patients". *The Oncologist Express*. May 2010. 15, 648-655.

<sup>89</sup> *CancerCare*. "Patient Values Initiative: The Many Voices of Value, A CancerCare Focus Group Assessment". 2017.

methodologically rigorous collection of population-level patient preferences data and its availability highlights an opportunity to identify and support initiatives that advance a standardized and rigorous collection and use of these data.

There are existing avenues that can encourage the collection of patient-centered data. In particular, the emergence and continuing growth of SDM requirements for coverage decisions can promote the collection of population-level patient preference data. Certain Medicare coverage determinations, such as those for implantable cardioverter defibrillator or screening for lung cancer with low dose computed tomography, require the adoption and documentation of SDM.<sup>90,91</sup>

Additionally, the FDA's CDRH ongoing Patient Preference Initiative (PPI) can serve as a regulatory channel to bolster the rigorous collection of patient preferences data. Designed to develop a systematic way to elicit, measure and incorporate patient preference information into medical device regulatory decisions, the PPI has begun to identify important benefits, risks, and tradeoffs from the patient perspective.<sup>92</sup> Researchers, patient advocacy organizations, and other stakeholders can support this initiative, and thus the broader aggregation of patient preference data for various patient populations, in different ways such as identifying tools that rigorously measure patient preference data or determining appropriate platforms in which to collect these data.

---

<sup>90</sup> Centers for Medicare & Medicaid Services. Decision Memo for Implantable Cardioverter Defibrillators (ICDs). February 2018

<sup>91</sup> Centers for Medicare & Medicaid Services. Decision Memo for Screening for Lung Cancer with Low Dose Computed Tomography (LDCT). February 2015.

<sup>92</sup> U.S. Food & Drug Administration. Patient Preference Initiative. September 2018.

# Appendix A

#	Criteria	Description	Must Have	Best Practice	Citation
1	Meaningfulness to Patients and Caregivers	The degree to which the instrument is capturing domains of information that actually matter to patients and/or caregivers. Evidence must exist to show that (1) patients were engaged during development of the instruments and (2) the questions asked in the PRO are considered by patients and/or caregivers to be relevant and meaningful for the disease/condition.	X		NQF. Measuring What Matters to Patients: Innovations in Integrating the Patient Experience into Development of Meaningful Performance Measures. 2017 Aug. 28.
2	Validity	The degree to which the content of the PRO actually reflects what is being measured			
2a		<p>Evidence must exist before a PRO is used. Show that the PRO construct and documentation delineate the intended application of the PRO in a given population.</p> <p>For FDA sample size for qualitative and quantitative studies for establishing content validity should be discussed with FDA</p>			<p>Reeve BB et al. ISOQOL recommends minimum standards for patient-reported outcome measures used in patient-centered outcomes and comparative effectiveness research. Qual Life Res. 2013 Oct;22(8):1889-905.</p> <p>FDA. Methods to Identify What is Important to Patients &amp; Select, Develop or Modify Fit-for-Purpose Clinical Outcomes Assessments. October 15- 16, 2018.</p> <p>Mokkink LB et al. The COSMIN study reached international consensus on taxonomy, terminology, and definitions of measurement properties for health-related patient-reported outcomes. J Clin Epidemiol. 2010 Jul;63(7):737-45.</p>

#	Criteria	Description	Must Have	Best Practice	Citation
2b	Construct validity	The degree to which a PRO relates to other measures (PROs, or Process measures). The PRO should be consistent with the hypothesis such as the internal relationship, relationships to scores of other instruments, or differences between groups. The PRO should consider whether there are empirical findings supporting differences in scores between known groups.	X		<p>Reeve BB et al. ISOQOL recommends minimum standards for patient-reported outcome measures used in patient-centered outcomes and comparative effectiveness research. <i>Qual Life Res.</i> 2013 Oct;22(8):1889-905.</p> <p>Mokkink LB et al. The COSMIN study reached international consensus on taxonomy, terminology, and definitions of measurement properties for health-related patient-reported outcomes. <i>J Clin Epidemiol.</i> 2010 Jul;63(7):737-45.</p> <p>National Quality Forum. Patient Reported Outcomes (PROs) in Performance Measurement. January 10, 2013.</p>
3	Reliability				
3a	Reliability testing type	<p>The degree to which a measure is free from measurement error using reliability testing such as interrelatedness among items in a multi-item PRO or possibly a test-retest, inter-rater, intra-rater reliability.</p> <p>A minimum reliability threshold of 0.70 is recommended. Sample sizes for testing should include at least 200 cases for a clinical trial and results should be replicated in at least one additional sample</p>	X		<p>Reeve BB. ISOQOL recommends minimum standards for patient-reported outcome measures used in patient-centered outcomes and comparative effectiveness research. <i>Qual Life Res.</i> 2013 Oct;22(8):1889-905.</p> <p>Frost MH. What is sufficient evidence for the reliability and validity of patient-reported outcome measures? <i>Value Health.</i> 2007 Nov-Dec;10 Suppl 2:S94-S105.</p>

#	Criteria	Description	Must Have	Best Practice	Citation
					National Quality Forum. Patient Reported Outcomes (PROs) in Performance Measurement. January 10, 2013.
3b	Psychometric testing	At least one full report on the development of the instrument and one on the use of the instrument are deemed necessary to evaluate the PRO psychometric properties. Risk does exist when no psychometric testing is performed especially in stage 3 trials.		X	Frost MH. What is sufficient evidence for the reliability and validity of patient-reported outcome measures? Value Health. 2007 Nov-Dec;10 Suppl 2:S94-S105.
4	Responsiveness	The PRO should detect changes in the construct being measured over time.	X		<p>Reeve BB et al. ISOQOL recommends minimum standards for patient-reported outcome measures used in patient-centered outcomes and comparative effectiveness research. Qual Life Res. 2013 Oct;22(8):1889-905.</p> <p>Mokkink LB et al. The COSMIN study reached international consensus on taxonomy, terminology, and definitions of measurement properties for health-related patient reported outcomes. J Clin Epidemiol. 2010 Jul;63(7):737-45.</p> <p>National Quality Forum. Patient Reported Outcomes (PROs) in Performance Measurement. January 10, 2013</p>

#	Criteria	Description	Must Have	Best Practice	Citation
5	Interpretability of Scores	Scores need to be easily interpreted by multiple stakeholders (e.g., clinicians, patients, researchers, policy makers). This should ensure that one can assign qualitative meaning to the quantitative scores or changes in scores.	X		<p>Reeve BB et al. ISOQOL recommends minimum standards for patient-reported outcome measures used in patient-centered outcomes and comparative effectiveness research. <i>Qual Life Res.</i> 2013 Oct;22(8):1889-905.</p> <p>Mokkink LB et al. The COSMIN study reached international consensus on taxonomy, terminology, and definitions of measurement properties for health-related patient-reported outcomes. <i>J Clin Epidemiol.</i> 2010 Jul;63(7):737-45.</p> <p>National Quality Forum. Patient Reported Outcomes (PROs) in Performance Measurement. January 10, 2013.</p>
		<p>The PRO could have:</p> <ul style="list-style-type: none"> <li>• reference/normative group benchmarks to provide a comparison score (e.g., high versus low score)</li> <li>• representative mean(s) and standard deviation(s) in the reference population</li> <li>• guidance on the minimally important difference in scores between groups and/or over time that can be considered meaningful from the patient and/or clinical perspective.</li> </ul>		X	<p>Reeve BB et al. ISOQOL recommends minimum standards for patient-reported outcome measures used in patient-centered outcomes and comparative effectiveness research. <i>Qual Life Res.</i> 2013 Oct;22(8):1889-905</p>

#	Criteria	Description	Must Have	Best Practice	Citation
6	PRO Translation	<p>The PRO need to be standardized and should have same wording when translated to different languages</p> <p>PROs could have cognitive interviews conducted to ensure that questions were appropriately translated</p> <p>PROs should include documentation of methods used to translate and evaluate the PRO measure in each language.</p>		X	<p>Reeve BB et al. ISOQOL recommends minimum standards for patient-reported outcome measures used in patient-centered outcomes and comparative effectiveness research. Qual Life Res. 2013 Oct;22(8):1889-905.</p> <p>National Quality Forum. Patient Reported Outcomes (PROs) in Performance Measurement. January 10, 2013.</p>
7	Burden				
7a	Patient Burden	<p>PRO questions should not be overly burdensome to patients (who may be ill or unable to complete long questionnaires or frequency of data collection may be disruptive)</p> <p>PROs should consider differences in literacy between patients</p> <p>Developers of PROs should make clear that the questions and response options are clear and easy to understand</p> <p>Qualitative testing should include patients who low literacy (e.g. 6<sup>th</sup> grade level reading)</p>	X		<p>Reeve BB et al. ISOQOL recommends minimum standards for patient-reported outcome measures used in patient-centered outcomes and comparative effectiveness research. Qual Life Res. 2013 Oct;22(8):1889-905.</p>

#	Criteria	Description	Must Have	Best Practice	Citation
7b	Researcher Provider Burden	Electronic PROs facilitate the ability to collect this information. However, may confound who is responding to the instrument.			Reeve BB et al. ISOQOL recommends minimum standards for patient-reported outcome measures used in patient-centered outcomes and comparative effectiveness research. Qual Life Res. 2013 Oct;22(8):1889-905.
8	Address Missingness of Data	Rules should be established and clearly delineated to prevent and monitor missing data. A valid statistical model should be used when dealing with missing data that accounts for uncertainty due to missing data. Should propose how to deal statistically with missing data and what efforts will be taken to mitigate.			PCORI. PCORI Methodology Standards. 2018.  FDA. Methods to Identify What is Important to Patients & Select, Develop or Modify Fit-for-Purpose Clinical Outcomes Assessments. October 15- 16, 2018.

## About Us

Avalere is a vibrant community of innovative thinkers dedicated to solving the challenges of the healthcare system. We deliver a comprehensive perspective, compelling substance, and creative solutions to help you make better business decisions. As an Inovalon company, we prize insights and strategies driven by robust data to achieve meaningful results. For more information, please contact [info@avalere.com](mailto:info@avalere.com). You can also visit us at [avalere.com](http://avalere.com).

## Contact Us

**Avalere Health**  
An Inovalon Company  
1350 Connecticut Ave, NW  
Washington, DC 20036  
202.207.1300  
[avalere.com](http://avalere.com)