PROs in Clinical Drug Development

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Healthcare Research Insights Inc.

February 27, 2019
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PROs in Clinical Drug Development

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Healthcare Research Insights Inc.
February 27, 2019

ISPOR Midwest Regional Chapter
Outline

• Introduction
• HEOR
• Definitions
• FDA and PROs
• Oncology
• Clinical Trials
• Conclusions
Introduction

• Objective: examine role of PROs in clinical drug development from the HEOR perspective, focusing on
  – US regulatory environment
  – Comparisons with Europe
  – Differences by therapeutic area
  – Practical considerations for clinical trial study design and communication
• “Health economics and outcomes research (HEOR) can help healthcare decision makers—including clinicians, governments, payers, health ministries, patients, and more—to adequately compare and choose among the available options.”

https://www.ispor.org/heor-resources/about-heor
Patient Reported Outcome (PRO)

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

• “Patient reported outcomes include health-related quality of life (HRQL), symptoms, utilities, and satisfaction ratings.”

Health-Related Quality of Life

FDA on health-related quality of life (HRQL)

• “HRQL is a multi-domain concept that represents the patient’s general perception of the effect of illness and treatment on physical, psychological, and social aspects of life.

• Claiming a statistical and meaningful improvement in HRQL implies: (1) that all HRQL domains that are important to interpreting change in how the clinical trial’s population feels or functions as a result of the targeted disease and its treatment were measured; (2) that a general improvement was demonstrated; and (3) that no decrement was demonstrated in any domain.”

QALY

Quality-adjusted life year (QALY)
• “measure of the state of health of a person or group in which the benefits, in terms of length of life, are adjusted to reflect the quality of life. One QALY is equal to 1 year of life in perfect health.”
• “Most widely used measure of benefit in cost-utility analysis”

Utility
• “measure of the preference or value that an individual or society gives a particular health state. It is generally a number between 0 (representing death) and 1 (perfect health)”

## FDA Responsibilities

<table>
<thead>
<tr>
<th></th>
<th>Safety</th>
<th>Effectiveness</th>
<th>Security</th>
<th>Regulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human and veterinary drugs, vaccines and other biological products for human use, and medical devices</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Food, cosmetics, dietary supplements, products that give off electronic radiation</td>
<td>✓</td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Tobacco products</td>
<td></td>
<td></td>
<td></td>
<td>✓</td>
</tr>
</tbody>
</table>

https://www.fda.gov/AboutFDA/WhatWeDo
2018 FDA Drug Approvals

• 59 NMEs (41 NDAs, 14 BLAs) approved
  – 29% oncology (65% orphan)
  – 58% orphan drugs
  – 71% first approved in US
  – 32% first in class
  – 73% priority approval
  – 41% fast track
  – 24% breakthrough

FDA Orphan Drug Program

• “provides orphan status to drugs and biologics .....that affect fewer than 200,000 people in the U.S., or that affect more than 200,000 persons but are not expected to recover the costs of developing and marketing a treatment drug.”

• “The traditional process for developing a new drug or biologic product .....estimated to cost between $800 million and $1.3 billion, and to take approximately 10–15 years.”


https://www.fda.gov/forindustry/developingproductsforrarediseasesconditions/default.htm
Institute of Medicine of the National Academies, Breakthrough Business Models, Drug Development for Rare and Neglected Diseases and Individualized Therapies, Workshop Summary, ©2009)
FDA and PROs

• PRO guidance in drug development: draft 2006, final 2009.

• January 2016 Pilot Clinical Outcome Assessment (COA) Compendium.
  – Part of effort to foster patient-focused drug development.
  – Contains clinical outcomes (including PROs) from the COA Qualification Program: December 31, 2015, and from approved drug labeling from 2003 to 2014.

## Pilot COA Compendium

<table>
<thead>
<tr>
<th>COLUMN</th>
<th>ELEMENTS</th>
<th>DESCRIPTION OF CONTENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Column 1</td>
<td>Disease/Condition</td>
<td>Lists disease or condition and any relevant FDA disease-specific guidance.</td>
</tr>
</tbody>
</table>
| Column 2 | Indication and/or Claim(s) Description | Lists key elements of indication and/or claim (either labeled or qualified). For ongoing COA qualification projects, targeted labeling or promotional claim(s) may not be yet known and may be described as “to be determined.”
*Inclusion of a clinical outcome assessment in the COA Compendium is not intended to indicate that the measure is or should be the sole (or primary) determinant of a clinical benefit in a particular clinical trial.* |
| Column 3 | Outcome of Interest      | Describes an outcome of interest that was assessed (labeled) or could be assessed (in our qualification program) by clinical outcome assessment(s) displayed in Column 4. |
| Column 4 | COA (COA Type)¹         | - Lists a labeled, qualified, or ongoing qualification project clinical outcome assessment name and/or description.                                                 |
|          |                           | - Includes the clinical outcome assessment type (i.e., a patient-reported outcome, observer-reported outcome, clinician-reported outcome, or performance outcome). |
| Column 5 | COA Context of Use       | Describes circumstances under which the outcomes of interest and the clinical outcome assessment have been used (i.e., labeled) or are targeted for use (i.e., they have been qualified or are part of an ongoing qualification). |
| Column 6 | COA Qualification Information | Lists ongoing and completed clinical outcome assessment qualification project information, if applicable.                                            |

FDA Development Resources, Clinical Outcome Assessment Compendium.
https://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/ucm459231.htm
Outcomes

COA outcome type

• Patient-reported outcome (PRO) measures
• Clinician-reported outcome (CRO) measures
• Observer-reported outcome (ORO) measures
• Performance outcome (PO) measures

https://www.fda.gov/drugs/developmentapprovalprocess/drugdevelopmenttoolsqualificationprogram/ucm284077.htm
Pilot COA Compendium

FDA Review Division

- Number of PROs greatest in Pulmonary, Allergy & Rheumatology (22) and Gastroenterology & Inborn Error (21).

- As percent of outcomes, PROs least frequent in Dermatology & Dental (13%) and Psychiatry (10%).

<table>
<thead>
<tr>
<th>Office</th>
<th>Review Division</th>
<th>PRO</th>
<th>ORO</th>
<th>CRO</th>
<th>PO</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>OAP</td>
<td>Anti-infective</td>
<td>6</td>
<td>7</td>
<td></td>
<td></td>
<td>13</td>
</tr>
<tr>
<td>OAP</td>
<td>Antiviral</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>OAP</td>
<td>Transplant &amp; Ophthalmology</td>
<td>2</td>
<td>5</td>
<td>2</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>ODE I</td>
<td>Cardiovascular &amp; Renal</td>
<td>5</td>
<td>7</td>
<td>3</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>ODE I</td>
<td>Neurology</td>
<td>8</td>
<td>4</td>
<td>15</td>
<td>5</td>
<td>32</td>
</tr>
<tr>
<td>ODE I</td>
<td>Psychiatry</td>
<td>2</td>
<td>1</td>
<td>16</td>
<td>1</td>
<td>20</td>
</tr>
<tr>
<td>ODE II</td>
<td>Anesthesia, Analgesia &amp; Addiction</td>
<td>7</td>
<td></td>
<td></td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>ODE II</td>
<td>Metabolism &amp; Endocrinology</td>
<td>3</td>
<td></td>
<td></td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>ODE II</td>
<td>Pulmonary, Allergy &amp; Rheumatology</td>
<td>22</td>
<td>12</td>
<td>5</td>
<td>39</td>
<td></td>
</tr>
<tr>
<td>ODE III</td>
<td>Dermatology &amp; Dental</td>
<td>1</td>
<td>7</td>
<td></td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>ODE III</td>
<td>Gastroenterology &amp; Inborn Error</td>
<td>21</td>
<td>3</td>
<td>5</td>
<td>29</td>
<td></td>
</tr>
<tr>
<td>ODE III</td>
<td>Bone, Reproductive and Urologic</td>
<td>7</td>
<td></td>
<td></td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>OHOP</td>
<td>Hematology</td>
<td>5</td>
<td>5</td>
<td></td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>OHOP</td>
<td>Oncology 1</td>
<td>2</td>
<td></td>
<td></td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>OHOP</td>
<td>Oncology 2</td>
<td>3</td>
<td></td>
<td></td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>96</td>
<td>5</td>
<td>77</td>
<td>21</td>
<td>199</td>
</tr>
</tbody>
</table>

* Table compiled from COA Compendium version 1 January 12, 2016. Includes specific outcomes only, excludes references to general industry guidance. For composite outcomes each component counted separately.

Pilot COA Compendium

- PROs were frequent outcomes (48%).
- Mostly from label claims (~ ¾), less frequently from COA Qualification Program (~ ¼).
- Most PRO assessments measured symptoms of disease, exceptions
  - SF-36 for rheumatoid arthritis.
  - Patient satisfaction with treatment for varicose veins.

**Pilot COA Compendium**

- PROs for pain (table), and less frequently fatigue, reported for multiple disease states; no standardization.
- COA Qualification Program submission source for 2 of 11 pain PROs.

<table>
<thead>
<tr>
<th>Disease/Condition</th>
<th>Outcome of Interest</th>
<th>Clinical Outcome Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ocular surgery</td>
<td>Absence of post-surgical ocular pain/discomfort</td>
<td>Visual analog scale and/or 6-point numeric pain scale</td>
</tr>
<tr>
<td>Chronic musculoskeletal pain</td>
<td>Pain intensity</td>
<td>Numerical pain rating scale or visual analog scale</td>
</tr>
<tr>
<td>Pain (acute)</td>
<td>Pain intensity</td>
<td>Numerical pain rating scale or visual analog scale</td>
</tr>
<tr>
<td>Pain (chronic)</td>
<td>Pain intensity</td>
<td>Numerical pain rating scale or visual analog scale</td>
</tr>
<tr>
<td>Pain (neuropathic)</td>
<td>Pain intensity</td>
<td>Numerical pain rating scale or visual analog scale</td>
</tr>
<tr>
<td>Pain (acute or chronic)</td>
<td>Pain intensity</td>
<td>QUALITE-Pain, COA Qualification Program submission U of Rochester, U of Washington</td>
</tr>
<tr>
<td>Psoriatic arthritis</td>
<td>Pain intensity</td>
<td>American College of Rheumatology (ACR) core set of outcome measures</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>Pain intensity</td>
<td>ACR core set of outcome measures</td>
</tr>
<tr>
<td>Irritable bowel syndrome-constipation</td>
<td>Abdominal pain intensity</td>
<td>11-point abdominal pain numeric rating scale</td>
</tr>
<tr>
<td>Prostate cancer (metastatic castration-resistant)</td>
<td>Pain intensity</td>
<td>Brief Pain Inventory Item #3 - Short Form</td>
</tr>
<tr>
<td>Plexiform neurofibromatosis 1</td>
<td>Tumor-related pain intensity and tumor-related pain interference</td>
<td>PN pain in children and adults, COA Qualification Program submission by NCI</td>
</tr>
</tbody>
</table>

HRQL Endpoints in RA Trials

<table>
<thead>
<tr>
<th>Instrument</th>
<th>Number of RCTs</th>
</tr>
</thead>
<tbody>
<tr>
<td>SF-36</td>
<td>16</td>
</tr>
<tr>
<td>SF-12</td>
<td>3</td>
</tr>
<tr>
<td>EQ5D</td>
<td>4</td>
</tr>
<tr>
<td>RAQoL</td>
<td>4</td>
</tr>
<tr>
<td>EUROHIS-QUOL8</td>
<td>1</td>
</tr>
</tbody>
</table>

*96 Randomized-controlled trials (RCTs) published from 2012 to 2014 (Phase 3 = 63), 44 of which assessed HRQL, all as secondary outcome. RAQoL = Rheumatoid Arthritis Quality of Life; SF-36 = Medical Outcomes Study Short Form-36; SF-12 = Short Form-12; EQ5D = EuroQoL 5D questionnaire; EUROHIS-QUOL8 = EUROHIS (World Health Organization) Quality of Life 8-item index.

## SF-36 in US Arthritis Drug Labeling

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Rheumatoid Arthritis</th>
<th>Psoriatic Arthritis</th>
<th>Ankylosing Spondylitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adalimumab</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Golimumab</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Tofacitinib</td>
<td>✓</td>
<td>✓</td>
<td></td>
</tr>
</tbody>
</table>

https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/125057s327lbl.pdf  
https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/125433s020s021lbl.pdf  
https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/203214s018lbl.pdf
American College of Rheumatology (ACR) response data in tofacitinib RA label

https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/203214s018lbl.pdf
HRQL in Analgesic Drug Development

HRQL discouraged as primary or secondary endpoint for pain drug development

Orphan Drug PRO Claims

2012-2016, more orphan drugs approved in US than EU.

- Smaller percentage of drugs had PRO labeling in US.
- HRQL labeling only in Europe.

<table>
<thead>
<tr>
<th>Agency</th>
<th>Total Orphan Drug Approvals</th>
<th>Approvals Meeting Study Criteria</th>
<th>Orphan Drugs with PRO Labeling</th>
<th>PRO Type</th>
<th>PRO Study Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Products</td>
<td>Indications</td>
<td>Symptoms</td>
</tr>
<tr>
<td>FDA</td>
<td>195</td>
<td>178</td>
<td>16 (9%)</td>
<td>16</td>
<td>16</td>
</tr>
<tr>
<td>EMA</td>
<td>56</td>
<td>53</td>
<td>12 (20%)</td>
<td>13</td>
<td>12</td>
</tr>
</tbody>
</table>

*Among 8 drugs with EMA HRQL label claim, 6 were oncology drugs, 7 had HRQL as a secondary endpoint and 1 as a tertiary endpoint. EORTC QLQ-C30 appeared 3 times, all other instruments appeared only once including FACT-O (Functional Assessment of Cancer Therapy – Ovarian), FACT-Lym (Functional Assessment of Cancer Therapy- Lymphoma) and SF-36.


FDA Guidance Oncology Endpoints

Clinical benefit endpoints for traditional approval

• Overall survival

• Symptom endpoints (patient-reported outcomes)
  – For symptom improvement, “symptoms should be assessed that are due to cancer rather than drug toxicity to the extent possible”. Patients need to be symptomatic at baseline.

• Disease-free survival, or event-free survival*

• Objective response rate, complete response*

• Progression-free survival, or time to progression*

*Also endpoints for accelerated approval.

FDA Oncology PRO Labeling

2010-2014, 40 FDA oncology drug approvals (160 total)

• 3 (7.5%) had PRO labeling, 2 in Clinical Studies and 1 in Adverse Reactions sections, all symptom scores.

• 13 (32.5%) had PRO data that was not included in labeling for various reasons; results not reported to FDA (3), inappropriate instruments (3), too many missing values (3) .... exploratory endpoint (1)

• Oncology drugs more likely to be orphan, fast track, with priority/accelerated review, and approved with smaller, open label, single-arm studies.

FDA vs. EMA Oncology PRO Labeling

2012 – 2016, FDA and EMA approved the same 49 oncology drugs with 64 indications.
- Submissions for 45 indications (70.3%) contained PRO data, mostly EORTC or FACT.
- FDA provided PRO feedback for 15 drugs (30.6%), but no PRO labeling.
- EMA granted PRO labeling for 19 (38.8%) drugs.
- Both agencies critical of excessive missing PRO data.
- FDA critical of content validity and single-arm, open-label study design.

EMA Oncology PRO Guidance

• June 2014 draft, reasons to include HRQL in development;
  – Patient focused assessment of disease burden and impact,
  – Understand treatment impact on functioning,
  – Complement efficacy and safety data,
  – Identify treatment-related symptoms that need management,
  – Differentiate two treatments with similar efficacy,
  – Facilitate more accurate patient-physician communication about quality of time remaining and treatment-related burden.
• Final document issued April 2016.

Oncology Physical Function PROs

108 published cancer trials measured PRO physical function

- EORTC QLQ-C30 (67% of studies)
  - First 5 items capture physical functioning
  - FDA 2009 PRO criteria: no formal patient input on item development

- SF-36, SF-20, and SF-12 (25% of studies)
  - 10, 6, and 2 physical function items, respectively
  - FDA 2009 PRO criteria: no formal patient input on item development or debriefing

Prostate Cancer Working Group 2
PRO Recommendations

Table 1. Validated prostate cancer-specific patient-reported outcome instruments*

<table>
<thead>
<tr>
<th>First author (reference)</th>
<th>Instrument</th>
<th>Domains</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clark (2)</td>
<td>Prostate Cancer Symptom Indices (31 items)</td>
<td>- Urinary incontinence (3 items) - Incontinence bother (1 item) - Obstruction (5 items) - Obstruction bother (5 items) - Bowel problems (6 items) - Bowel problems bother (4 items) - Sexual dysfunction (5 items) - Sexual problems (2 items)</td>
</tr>
<tr>
<td>Litwin (4)</td>
<td>UCLA Prostate Cancer Index (20 items)</td>
<td>- Urinary function (5 items) - Urinary bother (1 item) - Sexual function (3 items) - Sexual bother (1 item) - Bowel function (4 items) - Bowel bother (1 item)</td>
</tr>
<tr>
<td>Wei (3)</td>
<td>Expanded Prostate Cancer Index Composite (EPIC) (50 items)</td>
<td>- Urinary incontinence (4 items) - Urinary irritation/obstruction (7 items) - Overall urinary (1 item) - Sexual function (9 items) - Sexual bother (4 items) - Bowel function (7 items) - Bowel bother (7 items) - Hormonal function (5 items) - Hormonal bother (6 items)</td>
</tr>
</tbody>
</table>

Prostate Cancer Working Group 3
PRO Recommendations

• Pain intensity most established PRO in prostate cancer, use methods established by FDA (Basch 2014).
• Assess physical functioning using validated instrument, such as European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC QLQ-C30), or Patient-Reported Outcomes Measurement Information System (PROMIS).
• Collect patient-reported AEs using NCI’s Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE).

**HRQL in Prostate Cancer**

### Clinical Trials in Prostate Cancer Patients with Health-Related Quality of Life Endpoints

<table>
<thead>
<tr>
<th>Phase</th>
<th>Completed</th>
<th>Total</th>
<th>Percent Completed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase 2</td>
<td>86</td>
<td>263</td>
<td>32.7%</td>
</tr>
<tr>
<td>Phase 3</td>
<td>64</td>
<td>174</td>
<td>36.8%</td>
</tr>
<tr>
<td>Phase 4</td>
<td>11</td>
<td>26</td>
<td>42.3%</td>
</tr>
<tr>
<td>Phase 2 - 4</td>
<td>161</td>
<td>463</td>
<td>34.8%</td>
</tr>
<tr>
<td>All</td>
<td>297</td>
<td>922</td>
<td>32.2%</td>
</tr>
</tbody>
</table>

Searched ClinicalTrials.gov for “prostate cancer” and “quality of life” by study phase and in total. Trials may have included other cancer patients.
# HRQL in Prostate Cancer

<table>
<thead>
<tr>
<th>Trial</th>
<th>Prostate Cancer</th>
<th>Enrollment</th>
<th>Year</th>
<th>QOL Instrument(s)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>PROFIT</td>
<td>Localized</td>
<td>1,204</td>
<td>2017</td>
<td>Not specified</td>
<td>Secondary</td>
</tr>
<tr>
<td>PRECISION</td>
<td>Prostate Neoplasm</td>
<td>500</td>
<td>2017</td>
<td>EQ-5D-5L</td>
<td>Secondary</td>
</tr>
<tr>
<td>NCT00134056</td>
<td>Metastatic</td>
<td>1,038</td>
<td>2016</td>
<td>BPI, FACT-P</td>
<td>Other</td>
</tr>
<tr>
<td>NCT00138008</td>
<td>Prostate Cancer</td>
<td>200</td>
<td>2016</td>
<td>Not specified</td>
<td>Secondary</td>
</tr>
<tr>
<td>RADAR</td>
<td>Prostate Cancer</td>
<td>1,071</td>
<td>2017</td>
<td>EORTC QLQ-C30, EORTC QLQ-PR25</td>
<td>Secondary</td>
</tr>
<tr>
<td>NCT01810770</td>
<td>Prostatic Neoplasms</td>
<td>243</td>
<td>2017</td>
<td>FACT-P, EQ-5D, BPI-SF</td>
<td>Secondary</td>
</tr>
</tbody>
</table>

Selected from ClinicalTrials.gov search for “prostate cancer”, “quality of life”, “Phase 3” and “completed”.

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# PROs in Prostate Cancer

## PROs in Enzalutamide Randomized, Double-Blind, Controlled Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Comparator</th>
<th>Phase</th>
<th>N</th>
<th>PRO Instruments</th>
<th>PRO Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>AFFIRM</td>
<td>mCRPC</td>
<td>Placebo</td>
<td>III</td>
<td>1,199</td>
<td>FACT-P, BPI-SF</td>
<td>Secondary</td>
</tr>
<tr>
<td>PREVAIL</td>
<td>mCRPC</td>
<td>Placebo</td>
<td>III</td>
<td>1,717</td>
<td>FACT-P, EQ-5D, BPI-SF</td>
<td>Exploratory</td>
</tr>
<tr>
<td>STRIVE</td>
<td>CRPC</td>
<td>Bicalutamide</td>
<td>II</td>
<td>396</td>
<td>FACT-P</td>
<td>Secondary</td>
</tr>
<tr>
<td>TERRAIN</td>
<td>mCRPC</td>
<td>Bicalutamide</td>
<td>III</td>
<td>375</td>
<td>FACT-P, BPI-SF</td>
<td>Exploratory</td>
</tr>
</tbody>
</table>

BPI-SF = Brief Pain Inventory – Short Form, CRPC = castration-resistant prostate cancer, EQ-5D = European Quality of Life 5-Domain Scale, FACT-P = Functional Assessment of Cancer Therapy-Prostate, mCRPC = metastatic castration-resistant prostate cancer


STRIVE [https://clinicaltrials.gov/ct2/show/NCT01664923](https://clinicaltrials.gov/ct2/show/NCT01664923)


## PREVAIL PRO Data Assessments

<table>
<thead>
<tr>
<th>Agency</th>
<th>Median time to deterioration in FACT-P total score extended by 5.8 months relative to placebo (p&lt;0.001)</th>
<th>Decision driver</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gemeinsamer Bundesausschuss</td>
<td></td>
<td>May be of interest to patients</td>
</tr>
<tr>
<td>Scottish Medicines Consortium</td>
<td></td>
<td>Data were inconclusive</td>
</tr>
<tr>
<td>HAS</td>
<td></td>
<td>Not mention in their report</td>
</tr>
<tr>
<td>NICE National Institute for Health and Care Excellence</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

PROs in ASCO Value Framework

- ASCO value of cancer therapy framework first issued in 2015 to evaluate cancer drugs studied in prospective, randomized trials
  - Facilitate treatment discussions with patients in clinical setting
  - Bonus points for statistically significant improvement in cancer-related symptoms
- Updated in 2016 after receiving 400+ comments in 60-day period
  - Bonus points for statistically significant improvement in quality of life
  - “no substitute for rigorously measured PROs; the task force believes it is important to measure and report such variables and looks forward to amending the framework in the future to incorporate PROs when they are regularly reported as clinical trial end points.”

PRO Study Design

Maximize usefulness of PRO data for HEOR applications

• PRO instrument/study endpoints considerations
  – Select instrument(s) following appropriate guidance
  – Instrument preference can vary by country/region
  – Therapeutic area has major impact on PRO endpoint(s)
  – Don’t expect labeling for exploratory endpoints
  – Plan for indirect comparisons in health technology assessments

• No substitute for rigorous science
  – Understand published literature and ongoing trials
  – Integrate PRO into study protocol, manual, training, monitoring
  – Maximize data quality, while limiting study burden
  – Consider responder analysis

• Anticipate future data needs
## Patient Reported Outcomes

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Satisfaction</th>
<th>Health-Related Quality of Life (Utilities)</th>
</tr>
</thead>
<tbody>
<tr>
<td>May be primary endpoint</td>
<td>Not widely used</td>
<td>Secondary or exploratory endpoint</td>
</tr>
<tr>
<td>Items are clinically meaningful</td>
<td></td>
<td>Multi-dimensional, generate utilities from some instruments</td>
</tr>
<tr>
<td>Could be in US label</td>
<td></td>
<td>More likely to be in EU label, particularly useful for HTA</td>
</tr>
<tr>
<td>Broadly understood and accepted</td>
<td></td>
<td>Not well understood, challenging to communicate to non-experts</td>
</tr>
</tbody>
</table>
PRO Communication Plan: Investigators

• Rationale for PRO measures, particularly HRQL
  – Place of PROs in research, scientific rigor
  – What is going to be measured and why?
• Operational considerations
  – Specific instruments, subscales
  – Timing of PRO measurements
  – Minimizing missing data
• Analysis Plan
  – PRO endpoints
  – Clinically meaningful differences

• Reporting of results
  – Data findings
  – What does it mean?
• Uses of data
  – Registration filings
  – Scientific meetings and publications
  – HTA assessments
  – AMCP dossier
  – Clinical practice
  – Treatment pathways
  – Guidelines
Precision of HRQL Measurements

• Perception HRQL instruments not sufficiently reliable for individual treatment decisions.

• Used statistical criteria for instrument reliability and precision, measurement error comparable in common clinical and HRQL measures, e.g.
  – Classification of vital sign measurements ranged from high reliability for tachycardia ($K=0.85$) to low reliability for systolic hypotension ($K=0.27$).
  – SF-36 subscale measurements ranged from high reliability for physical functioning ($K=0.93$) to low reliability for social functioning ($K=0.60$).

## Correlation of Clinical & HRQL Data

### Associations of Other Clinical and HRQL Variables in Cystic Fibrosis

<table>
<thead>
<tr>
<th>Source</th>
<th>Other Clinical Measure</th>
<th>Correlation with HRQL (QWB, SIP)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physiological</td>
<td>Arterial oxygen saturation ( \text{Sao}_2 )</td>
<td>0.40</td>
</tr>
<tr>
<td>Physiological</td>
<td>Forced expiratory volume in 1 second ( \text{FEV}_1 )</td>
<td>0.33-0.40</td>
</tr>
<tr>
<td>Clinician reported</td>
<td>Maximal capacity exercise</td>
<td>0.57</td>
</tr>
<tr>
<td>Patient reported</td>
<td>MRC dyspnea scale</td>
<td>0.75</td>
</tr>
</tbody>
</table>

*Correlation coefficients (r) from review of literature.

MRC = Medical Research Council; QWB = Quality of Well-Being; SIP = Sickness Impact Profile

Patients and PROs

- “Patient-reported outcomes provide additional information on treatment effects and patient perceptions that are not adequately captured by objective criteria and clinician reported outcomes.”
- Symptom severity at a point in time may not reflect patient’s HRQL, e.g. anxiety about future IBD fares.
- In some conditions (e.g. oncology, heart failure, COPD and RA) baseline HRQL physical domains scores predict survival

SPIRIT-PRO

• Standard Protocol Items: Recommendations for Intervventional Trials (SPIRIT)
  – 2013 protocol checklist
• Updated in 2018 to include PRO-specific issues
  – Improve quality of PRO evidence from clinical trials
  – 38 international partner organizations participated

SPIRIT-PRO

- 11 PRO extensions
  - Trial rationale
  - Objectives
  - Eligibility criteria
  - Evaluation of intervention
  - Time points for assessment
  - Instrument selection and measurement properties
  - Data collection plan
  - Translation to other languages
  - Proxy completion
  - Strategies to minimize missing data
  - Monitoring

- 5 PRO elaborations
  - Specify responsible person
  - Sample size/power
  - Assessment for participant discontinuations/deviations,
  - Statistical analysis plan
  - Plan for missing data imputation/sensitivity analyses

CONSORT PRO

• Consolidated Standards of Reporting Trials (CONSORT) issued in 1996 and updated in 2010
  – Endorsed by major journals
  – Improves completeness of RCT reporting

• 2013 CONSORT PRO checklist for RCTs in which PROs are primary or important secondary outcome
  – Identify PRO as primary or secondary outcome in abstract
  – Describe PRO hypothesis and relevant domains
  – Provide evidence of instrument validity and reliability
  – Explicitly state statistical approach for missing data
  – Discuss limitations and generalizability of PRO findings

Conclusions

PROs in clinical drug development from HEOR perspective

• US regulatory environment
  – PRO label claims not common
  – FDA more receptive to patient-reported symptoms than HRQL
  – PRO acceptance varies by FDA review division/therapeutic area
    – Could be primary registration outcome (e.g. pain intensity)
    – Labeling may included HRQL (e.g. arthritis)
• EMA more likely to approve HRQL labeling
• With therapeutic area “maturity” of HRQL research varies by disease/condition
• HTA agencies apply different criteria when assessing PRO data
• Acceptance of HRQL by clinical community is critical
• Practical considerations for study design and communication
  – Treat PROs as a sub-study
  – Rationale and hypothesis needs to be explicit
  – Minimize missing data
  – PRO communication begins with investigators
  – Follow clinical and PRO guidance, SPIRIT-PRO and CONSORT PRO checklists