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PROs in Clinical Drug Development

Annette Champion, MBA
Healthcare Research Insights Inc.

February 27, 2019

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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

HEOR

- “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

Definitions

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. "[1]
- "Patient reported outcomes include health-related quality of life (HRQL), symptoms, utilities, and satisfaction ratings." [2]

1. http://wayback.archive-it.org/7993/20180424212148/https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/ucm370262.htm#pro

2. Calvert M, Blazeby J, Altman DG, et al. Reporting of patient-reported outcomes in randomized trials: the CONSORT PRO extension. JAMA 2013;309:814–822. PMID: 23443445. doi: 10.1001/jama.2013.879.

Definitions

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."

http://wayback.archive-it.org/7993/20180424212148/https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/ucm370262.htm#pro

Definitions

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)”

National Institute for Health and Care Excellence (NICE) Glossary https://www.nice.org.uk/glossary?letter=q

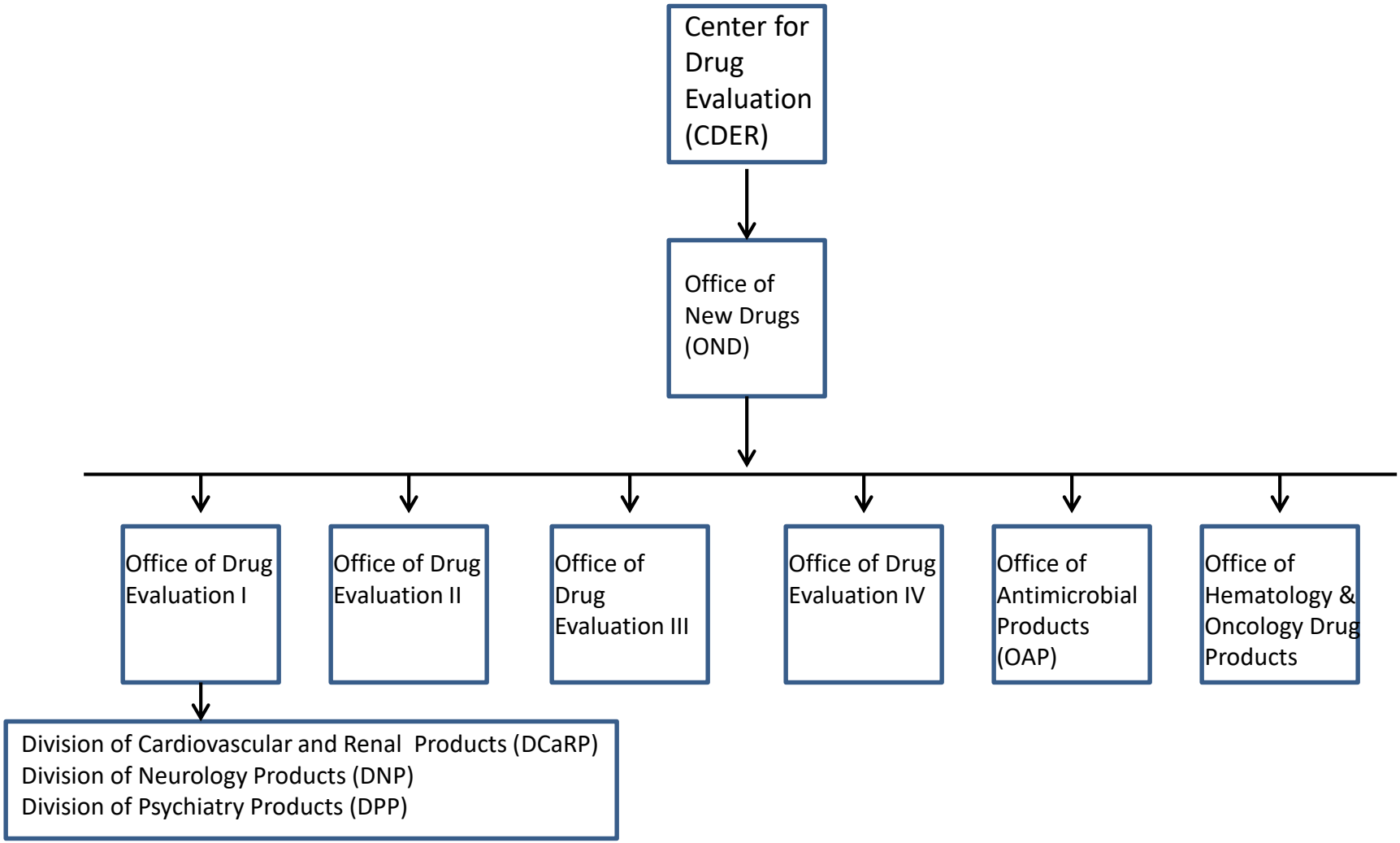
FDA

FDA Responsibilities

	Safety	Effectiveness	Security	Regulation
Human and veterinary drugs, vaccines and other biological products for human use, and medical devices	√	√	√	
Food, cosmetics, dietary supplements, products that give off electronic radiation	√		√	
Tobacco products				√

https://www.fda.gov/AboutFDA/WhatWeDo

FDA Office of New Drugs



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

Center for Drug Evaluation and Research, Advancing Health Through Innovation 2018 New Drug Therapy Approvals. https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DrugInnovation/UCM629290.pdf

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."
- Incentives added in 2007 to 1983 Orphan Drug Act.

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 Individuallized Therapies, Workshop Summary, ©2009)
https://www.ncbi.nlm.nih.gov/books/NBK50977/pdf/Bookshelf_NBK50977.pdf

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.

Guidance for Industry Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims. FDA; CDER, CBER, CDRH. December 2009. https://www.fda.gov/downloads/drugs/guidances/ucm193282.pdf
FDA Development Resources, Clinical Outcome Assessment Compendium. https://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/ucm459231.htm

Pilot COA Compendium

COLUMNS	ELEMENTS	DESCRIPTION OF CONTENT
Column 1	Disease/Condition	Lists disease or condition and any relevant FDA disease-specific guidance.
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%).

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

* 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.

OAP = Office of Antimicrobial Products, ODE = Office of Drug Evaluations, OHOP = Office of Hematology & Oncology Products; PRO = patient-reported outcome, ORO = observer-reported outcome, CRO = clinician-reported outcome, PO = performance outcome

A. Champion. PHP218 Patient Reported Outcomes within the FDA COA Qualification Program. *Value in Health* 20 (2017) A53.

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.

A. Champion. PHP218 Patient Reported Outcomes within the FDA COA Qualification Program. *Value in Health* 20 (2017) A53.

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.

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

A. Champion. PHP218 Patient Reported Outcomes within the FDA COA Qualification Program. *Value in Health* 20 (2017) A53.

HRQL Endpoints in RA Trials

Rheumatoid Arthritis Randomized-Controlled Trials with HRQL Published 2012-2014 (n=44)*	
Instrument	Number of RCTs
SF-36	16
SF-12	3
EQ5D	4
RAQoL	4
EUROHIS-QUOL8	1

*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.

Orbai AM and Bingham CO. Patient Reported Outcomes in Rheumatoid Arthritis Clinical Trials. *Curr Rheumatol Rep* 2015. 17(4): 501. doi:10.1007/s11926-015-0501-8

Arthritis Drug Labeling

SF-36 in US Arthritis Drug Labeling			
	Indication		
Generic Name	Rheumatoid Arthritis	Psoriatic Arthritis	Ankylosing Spondylitis
Adalimumab	√	√	√
Golimumab	√	√	√
Tofacitinib	√	√	

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

ACR Response Criteria

American College of Rheumatology (ACR) response data in tofacitinib RA label

https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/203214s018lbl.pdf

Table 3: Trial 1 — Components of ACR Response at Week 14

	Trial 1 Active RA, despite MTX	
	Placebo + MTX	**SIMPONI ARIA + MTX**
N[a]	197	395
Number of swollen joints (0-66)		
Baseline	15	15
Week 14	11	6
Number of tender joints (0-68)		
Baseline	26	26
Week 14	20	13
Patient's assessment of pain (0-10)		
Baseline	6.5	6.5
Week 14	5.6	3.9
Patient's global assessment of disease activity (0-10)		
Baseline	6.5	6.5
Week 14	5.5	4.0
Physician's global assessment of disease activity (0-10)		
Baseline	6.3	6.2
Week 14	4.9	3.1
HAQ score (0-3)		
Baseline	1.6	1.6
Week 14	1.4	1.1
CRP (mg/dL) (0-1)		
Baseline	2.2	2.8
Week 14	1.8	0.9

Note: All values are means.
[a]N reflects randomized patients; actual number of patients evaluable for each endpoint may vary.

HRQL in Analgesic Drug Development

HRQL discouraged as primary or secondary endpoint for pain drug development

c. Health-related quality of life

Health-related quality of life (HRQL) is a multidomain concept that represents the subject's overall perception of the effect of an illness and its treatment. An HRQL measure captures, at a minimum, physical, psychological (including emotional and cognitive), and social functioning. In general, HRQL instruments are not appropriate as primary endpoints for several reasons: (1) some HRQL instruments include inappropriate items for drug development trials (e.g., financial well-being); (2) concepts and domains measured are distal to the effect of treatment; (3) the proximal effects of treatment on how subjects feel and function may not be captured (e.g., items reflecting personal well-being may be too far *downstream* to reflect treatment benefit); and (4) they reflect or respond to other causal factors that increase variability of the measurement and impair the interpretation of treatment effect.

The inclusion of distal attributes of well-being that typify HRQL questionnaires attenuate the overall ability of the measure to detect change. This occurs even when improvements in personal well-being items more securely reflect treatment benefits. Even expected improvements in personal relationships or social participation can be less likely to show change across the duration of the clinical trial. A claim based on HRQL measurement to demonstrate investigational treatment benefit can be misleading if treatment adverse effects are not yet fully known and the HRQL instrument does not prospectively measure the effect of relevant adverse effects on HRQL. Overall, HRQL is inappropriate as a primary endpoint, likely challenging as a secondary endpoint, but certainly welcome as an exploratory endpoint when an instrument addresses concepts about which subjects express concern.

Guidance for Industry Analgesic Indications: Developing Drug and Biologic Products. Draft Guidance, February 2014.
https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm384691.pdf

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.

Orphan Drug PRO Label Claims in US and Europe, 2012 - 2016

Agency	Total Orphan Drug Approvals	Approvals Meeting Study Criteria	Orphan Drugs with PRO Labeling		PRO Type			PRO Study Endpoint	
			Products	Indications	Symptoms	Physical Function	HRQL	Primary	Secondary
FDA	195	178	16 (9%)	16	16	2	0	14	2
EMA	56	53	12 (20%)	13	12	5	8*	4	8

*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.

Jarosławski, et. al. Low rates of patient-reported outcome claims for orphan drugs approved by the US Food and Drug Administration. *Journal of Market Access & Health Policy*. 2018;6,1433426.
Jarosławski, et. al. Patient-reported outcome claims in European and United States orphan drug approvals. *Journal of Market Access & Health Policy*. 2018;6,1542920.

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.

Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, Guidance for Industry. December 2018. https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071590.pdf

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.

Gnanasakthy A, et. al. Patient-Reported Outcomes Labeling for Products Approved by the Office of Hematology and Oncology Products of the US Food and Drug Administration (2010 – 2014). J Clin Oncol 34, published ahead of print on April 11, 2016.

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.

Gnanasakthy A, et. al. PRO labeling for oncology drugs approved by FDA and EMA, 2012 – 2016. *J Clin Oncol* 2018. 36.15 suppl.e18730.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Oncology

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.

https://www.ema.europa.eu/documents/scientific-guideline/draft-reflection-paper-use-patient-reported-outcome-pro-measures-oncology-studies_en.pdf
https://www.ema.europa.eu/documents/other/appendix-2-guideline-evaluation-anticancer-medicinal-products-man_en.pdf

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

Atkinson TM, et. al. Patient-Reported Physical Function Measures in Cancer Clinical Trials. *Epidemiology Reviews*. 2017;39.59-70.

Prostate Cancer Working Group 2 PRO Recommendations

Oncology

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

First author (reference)	Instrument	Domains
Clark (2)	Prostate Cancer Symptom Indices (31 items)	- 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)
Litwin (4)	UCLA Prostate Cancer Index (20 items)	- Urinary function (5 items) - Urinary bother (1 item) - Sexual function (8 items) - Sexual bother (1 item) - Bowel function (4 items) - Bowel bother (1 item)
Wei (3)	Expanded Prostate Cancer Index Composite (EPIC) (50 items)	- 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)

Chen RC, et. al. Recommended Patient-Reported Core Set of Symptoms to Measure in Prostate Cancer Treatment Trials. JNCI 2014. 106(7):dju132 doi:10.1093/jnci/dju132.

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).

Scher HI, Morris MJ, Stadler WM, et al. Trial design and objectives for castration-resistant prostate cancer: updated recommendations from the prostate cancer clinical trials working Group 3. *J Clin Oncol.* 2016;34(12):1402–1418.

HRQL in Prostrate Cancer

Clinical Trials in Prostate Cancer Patients with Health-Related Quality of Life Endpoints			
	Number of Studies		
	Completed	Total	Percent Completed
Phase 2	86	263	32.7%
Phase 3	64	174	36.8%
Phase 4	11	26	42.3%
Phase 2 - 4	161	463	34.8%
All	297	922	32.2%
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

Selected Phase 3 Studies in Prostate Cancer Patients with HRQL Endpoints Completed 2016 - 2017					
Trial	Prostate Cancer	Enrollment	Year	QOL Instrument(s)	Outcome
PROFIT	Localized	1,204	2017	Not specified	Secondary
PRECISION	Prostate Neoplasm	500	2017	EQ-5D-5L	Secondary
NCT00134056	Metastatic	1,038	2016	BPI, FACT-P	Other
NCT00138008	Prostate Cancer	200	2016	Not specified	Secondary
RADAR	Prostate Cancer	1,071	2017	EORTC QLQ-C30, EORTC QLQ-PR25	Secondary
NCT01810770	Prostatic Neoplasms	243	2017	FACT-P, EQ-5D, BPI-SF	Secondary

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

PROs in Prostate Cancer

PROs in Enzalutamide Randomized, Double-Blind, Controlled Trials						
Study	Population	Comparator	Phase	N	PRO Instruments	PRO Endpoint
AFFIRM	mCRPC	Placebo	III	1,199	FACT-P, BPI-SF	Secondary
PREVAIL	mCRPC	Placebo	III	1,717	FACT-P, EQ-5D, BPI-SF	Exploratory
STRIVE	CRPC	Bicalutamide	II	396	FACT-P	Secondary
TERRAIN	mCRPC	Bicalutamide	III	375	FACT-P, BPI-SF	Exploratory

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

Luo J and Graff JN. Impact of enzalutamide on patient-related outcomes in metastatic castration-resistant prostate cancer: current perspectives. Research and Reports in Urology 2016. 8;217-224.
STRIVE https://clinicaltrials.gov/ct2/show/NCT01664923
TERRAIN https://www.ncbi.nlm.nih.gov/pubmed/27497762?dopt=Abstract
Heidenreich A, et. al. Impact of Enzalutamide Compared with Bicalutamide on Quality of Life in Men with Metastatic Castration-resistant Prostate Cancer: Additional Analyses from the TERRAIN Randomised Clinical Trial. *Eur Urol* 2017. 71;534-542.

Oncology

PREVAIL PRO Data Assessments

Agency	Median time to deterioration in FACT-P total score extended by 5.8 months relative to placebo (p<0.001)
Gemeinsamer Bundesausschuss	Decision driver
Scottish Medicines Consortium	May be of interest to patients
HAS HAUTE AUTORITÉ DE SANTÉ	Data were inconclusive
NICE National Institute for Health and Care Excellence	Not mention in their report

Issue Panel: Prove it with PROs, November 12, 2018, ISPOR European Conference, Barcelona, Spain. The Industry Perspective, Stefan Holmstrom, Astellas. https://www.ispor.org/docs/default-source/presentations/86891pdf.pdf?sfvrsn=5840145d_0

ASCO
AMERICAN SOCIETY OF CLINICAL ONCOLOGY

Oncology

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."

Schnipper LE et. al. Updating the American Society of Clinical Oncology Value Framework: Revisions and Reflections in Response to Comments Received. *J Clin Oncol* 2016. 34; 2925-2934.
https://www.asco.org/about-asco/press-center/news-releases/asco-value-framework-update

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

Symptoms	Satisfaction	Health-Related Quality of Life (Utilities)
May be primary endpoint	Not widely used	Secondary or exploratory endpoint
Items are clinically meaningful		Multi-dimensional, generate utilities from some instruments
Could be in US label		More likely to be in EU label, particularly useful for HTA
Broadly understood and accepted		Not well understood, challenging to communicate to non-experts

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).

Hahn EA et. al. Precision of Health-Related Quality-of-Life Data Compared with Other Clinical Measures. *Mayo Clin Proc* 2007.82;1244-1254.

Correlation of Clinical & HRQL Data

Associations of Other Clinical and HRQL Variables in Cystic Fibrosis		
Source	Other Clinical Measure	Correlation with HRQL (QWB, SIP)*
Physiological	Arterial oxygen saturation (Sao_2)	0.40
Physiological	Forced expiratory volume in 1 second (FEV_1)	0.33-0.40
Clinician reported	Maximal capacity exercise	0.57
Patient reported	MRC dyspnea scale	0.75

*Correlation coefficients (r) from review of literature.
MRC = Medical Research Council; QWB = Quality of Well-Being; SIP = Sickness Impact Profile

Hahn EA et. al. Precision of Health-Related Quality-of-Life Data Compared with Other Clinical Measures. *Mayo Clin Proc* 2007.82;1244-1254.

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

Hahn EA et. al. Precision of Health-Related Quality-of-Life Data Compared with Other Clinical Measures. *Mayo Clin Proc* 2007.82;1244-1254.

SPIRIT-PRO

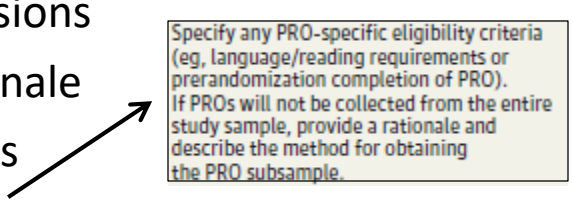
- Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT)
  - 2013 protocol checklist
- Updated in 2018 to include PRO-specific issues
  - Improve quality of PRO evidence from clinical trials
  - 38 international partner organizations participated

Calvert M, et. al. Guidelines for Inclusion of Patient-Reported Outcomes in Clinical Trial Protocols, The SPIRIT-PRO Extension. *JAMA* 2018. 319:483-494.

Clinical Trials

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

Calvert M, et. al. Guidelines for Inclusion of Patient-Reported Outcomes in Clinical Trial Protocols, The SPIRIT-PRO Extension. *JAMA* 2018. 319:483-494.

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

Calvert M, et. al. Reporting of Patient-Reported Outcomes in Randomized Trials, The CONSORT PRO Extension. *JAMA* 2013. 309;814-822.

Conclusions

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

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