

Patient Reported Endpoints and the Relevance to Payers and Regulators: Is There Agreement?

***SIXTH ANNUAL
PATIENT-REPORTED OUTCOME CONSORTIUM WORKSHOP***

April 29 - 30, 2015 ■ Silver Spring, MD



The views and opinions expressed in the following slides are those of the individual presenters and should not be attributed to their respective organizations/companies, the U.S. Food and Drug Administration, the Critical Path Institute, the PRO Consortium, or the ePRO Consortium.

These slides are the intellectual property of the individual presenters and are protected under the copyright laws of the United States of America and other countries. Used by permission. All rights reserved. All trademarks are the property of their respective owners.

Objective

- To understand the relevance of patient-reported endpoints to payers and regulators
 - The incremental value of a PRO based claim
 - Is there a difference between payers and regulators?
 - Are there endpoints that are of greater relevance? The relative value of some PROs over others.
 - Is there a magnitude of benefit that is meaningful and understood?
Meaningful change and responder definitions

Outline

- Introduction
- Incremental value of PRO based label claims
- Value of PROs in Oncology HTAs-survey output
- Similarities and differences between US and EU: are there insights to be gained?
- Panel discussion with FDA and members of payer organizations
- Q & A

Moderator

- Peter C. Trask, Ph.D., MPH, Principal PCOR Scientist, Genentech

Presenter and Panelists

- David S. Reasner, PhD – Vice President, Data Science & Head, Study Endpoints, Ironwood Pharmaceuticals
- Vasudha Bal, MSc, MBA – Director, PRO, Novartis Pharmaceuticals
- Katarina Halling, MSc – PRO Group Director, AstraZeneca
- Selena Daniels, PharmD, MS – Study Endpoints Reviewer, Study Endpoints and Labeling Development, FDA
- Alan L. Shields, PhD – Vice President, Endpoint Development and Outcomes Assessment, Adelphi Values
- Robin S. Turpin, PhD – Director and Head, US HEOR, US Medical and Scientific Affairs, Takeda Pharmaceuticals

Linking Payers & Regulators – The PRO Claim

David S. Reasner, Ph.D.
Ironwood Pharmaceuticals

***SIXTH ANNUAL
PATIENT-REPORTED OUTCOME CONSORTIUM WORKSHOP***

April 29 - 30, 2015 ■ Silver Spring, MD

Introducing the PRO Guidance: Key Aspects



- “For the FDA to provide useful early input, sponsors should provide their **labeling goals**, a hypothesized PRO instrument **conceptual framework**, and the relationship of the PRO endpoints to other clinical trial endpoints in **preliminary endpoint models** for the planned confirmatory trials.”



Labeling Goals

Guidance Appendix – The “Dossier” [eCTD 5.3.5.3]



Sections

- I. Instrument
- II. Targeted Claims or TPP
- III. Endpoint Model
- IV. The PRO Instrument’s Conceptual Framework
- V. Content Validity Documentation
- VI. Assessment of Other Measurement Properties
- VII. Interpretation of Scores
- VIII. Language Translation and Cultural Adaptation
- IX. Data Collection Method
- X. Modifications
- XI. PRO-Specific Plans Related to Clinical Trial Design and Data Analysis
- XII. Key References

Appendix A – User Manual

Appendix B – Item Tracking Matrix

Appendix C - Transcripts



Target Product Profile — A Strategic Development Process Tool



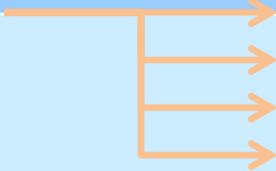
Key Section List

1. **Indications and Usage**
2. **Dosage and Administration**
3. **Dosage Forms and Strengths**
4. **Contraindications**
5. **Warnings and Precautions**
6. **Adverse Reactions**
7. **Drug Interactions**
8. **Use in Specific Populations**
9. **Drug Abuse and Dependence**
10. **Overdosage**
11. **Description**
12. **Clinical Pharmacology**
13. **Nonclinical Toxicology**
14. **Clinical Studies**
15. **References**
16. **How Supplied/Storage and Handling**
17. **Patient Counseling Information**



PRO Claim with a Supportive Concept



Concept	Link	Endpoint
Indication:		Primary:
Treatment of Disease X		Physiological Effect
Supportive Concepts:		Secondary:
Improvement in Symptoms/Signs of Disease X		Symptoms Diary [PRO] Signs Diary [PRO] Physical Exam Physical Performance [Possible PRO]



PRO Claim with an Indication

Concept	Link	Endpoint
Indication:		Primary:
Treatment of Symptoms of Disease Y		Total Disease Y Symptoms Score [PRO]
Supportive Concepts:		Secondary:
Other Treatment Benefit		Physical Performance [Possible PRO] Disease Y-related Physical Limitations [PRO]

An Aligned Conceptual Framework Supports Labeling Claims



- “For example, in clinical trials of functional disorders defined by clusters of specific symptoms and signs, a PRO instrument consisting of **a single-item global question usually would be inadequate as an endpoint to support labeling claims** and would be uninformative about the effects on each specific symptom and sign. Instead, the effect of treatment on each of the appropriate symptoms and signs should be adequately measured.”
- “**A multidomain PRO measure may successfully support a labeling claim based on one or a subset of the domains** measured if an *a priori* analysis plan prespecifies the domains that will be targeted as endpoints and the method of analysis that will adjust for the multiplicity of tests for the specific claim. The use of domain subsets as clinical trial endpoints presupposes that the PRO instrument was adequately developed and validated to measure the subset of domains independently from the other domains.”



Endpoint Model: Define the Role

- “Sponsors should define the role a PRO endpoint is intended to play in the clinical trial (i.e., a primary, key secondary, or exploratory endpoint) so that the instrument development and performance can be reviewed in the context of the intended role, and appropriate statistical methods can be planned and applied. It is critical to plan these approaches in what can be called an endpoint model.
- **“PRO instrument adequacy depends on its role as depicted in the endpoint model. The endpoint model explains the exact demands placed on the PRO instrument to attain the evidence to meet the clinical trial objectives and support the targeted claims corresponding to the concepts measured.”**



Endpoint Model: Hierarchy

- **“A single hierarchy of endpoints as diagrammed in an endpoint model (see Figures 1 and 2 in section III.A., Endpoint Model) is determined by the trial’s stated objectives and the clinical relevance and importance of each specific measure independently and in relationship to each other.”**

Concept	Link	Endpoint
Indication:		Primary:
Treatment of Disease X		Physiological Effect
Supportive Concepts:		Secondary:
Improvement in Symptoms/Signs of Disease X		Symptoms Diary [PRO] Signs Diary [PRO] Physical Exam Physical Performance [Possible PRO]



Endpoint Model: Corner Pocket?

- “We intend to determine the adequacy of clinical trial data to support claims in light of the **prespecified method** for endpoint analysis. We usually view unplanned or *post hoc* statistical analyses conducted **after unblinding as exploratory** and, therefore, unable to serve as the basis of a labeling claim of effectiveness.”
- “It is critical that the clinical trial protocol define the endpoint measures and the criteria for the statistical analysis and interpretation of results, including a **specification of the conditions for a positive clinical trial** conclusion, because determination of these criteria and conditions after data are unblinded will not be credible.”



The PRO Claim: But what can I say?

- Under the FFD&C Act and FDA's implementing regulations, promotional pieces making claims:
 - Must be consistent with approved product labeling
 - Must be supported by **substantial evidence**
 - Must not be false or misleading
 - Must have balance between efficacy and risk information
 - Must reveal all material information
- **For example, brochures, sales aids, mailing pieces & slide decks accompanied by package insert**



The PRO Claim: But what can I say?



- **The Study Endpoints Team should deliver...**
 - **Aspirational TPP that identifies differentiating MOA, formulation, dose, etc.**
 - **Well-defined and reliable clinical outcome assessment(s)**
 - **Pre-specified endpoint(s) with Substantial evidence**
 - **Clinically-meaningful improvement (e.g., mean difference accompanied by an interpretable CDF plot)**

Potential Outcome: An approved indication and clinical trial section of label to aid the communication of the PRO claim in compliance with the FFD&C Act

- **“But what can I say?”**



The PRO Claim: Summary



- **Begin by outlining the hypothesized concepts and potential claims – The End**
 - For example, “**Drug X** is indicated for the treatment of insomnia. **Drug Y** has been shown to decrease Sleep Latency and improve Sleep Maintenance.”
- **Place the PRO(s) within a preliminary endpoint model to obtain early input**
- **Align the targeted indication with the corresponding assessment (what we measure) and endpoint (what we analyze)**
- **Build an endpoint model *a priori* to support your claims, including “HEOR” endpoints for payers.**

Payer Perceptions of Patient- Reported Outcomes in Health Care Decision Making

Vasudha Bal
Novartis

***SIXTH ANNUAL
PATIENT-REPORTED OUTCOME CONSORTIUM WORKSHOP***

April 29 - 30, 2015 ■ Silver Spring, MD



Session Outline/Objective

- **OBJECTIVES:** To determine how impactful patient-reported outcome (PRO) data are on market access decision making.
- **METHODS:**
 - Targeted literature review was done - PubMed and Embase as well as drug approval packages in FDA, EMA, NICE, HAS, IQWiG databases.
 - One-on-one semistructured interviews were conducted with 16 leading payers and payer advisors around the world.
 - An online survey was developed to examine the value, from the payer perspective, of PRO data in HTA. The survey was open from December 8, 2014, to March 4, 2015, with 20 surveys completed.

Payer Participants in One-on-One Interviews



United States 	Geographic Coverage Area	Covered Lives			
		Total (Millions)	Commercial	Medicare	Medicaid
Medical director	National	11.0 ^a	35%	43%	5% Medicaid 17% Tricare
Pharmacy director	National	35.0	70%	15%	15%
Medical director	Employer payer	0.5	100%	0%	0%

Ex-US	Payer Advisor Profile	
Australia 	Health economics professor and advisor to Medical Services Advisory Committee (MSAC) and Pharmaceutical Benefits Advisory Committee (PBAC)	
Brazil 	Clinical oncologist, professor, and advisor to private insurance providers	
France 	Health economics professor and advisor to Haute Autorité de Santé (HAS)	
Germany 	Health economics professor and member of the arbitration board for drug prices in the statutory health insurance	
Italy 	Health economics professor and advisor to regional health agency (Lombardy, Lazio, Local/Hospital)	
Korea 	Health economics professor and advisor to Health Insurance Review and Assessment (HIRA)	
Netherlands 	HTA professor and advisor to Zorginstituut Nederland (ZINL, formerly CVZ)	
Poland 	Professor and advisor to Agencja Oceny Technologii Medycznych (AOTM)	
Spain 	Health economics professor and advisor to regional health authorities (Andalucia)	
Sweden 	Health economics professor and advisor to Tandvårds- och läkemedelsförmånsverket (TLV)	
Taiwan 	Health economics professor and HTA advisor	
Turkey 	Health economics professor and advisor to public and private insurance providers	
United Kingdom 	Health economics professor and advisor to the National Institute for Health and Care Excellence (NICE)	

Payer Participants in Online Survey



Country	Completed Surveys	Partially Completed Surveys (Last Question in Parentheses)
Australia 	0	1 (Q9)
China 	1	0
France 	1	0
Germany 	1	0
South Korea 	0	1 (Q2)
Spain 	2	0
Taiwan 	1	0
United Kingdom 	1	0
United States 	5 pharmacy directors 8 medical directors	2 pharmacy directors (Q1, Q9) 3 medical directors (Q2, Q4, Q9)
Total	20	7

- HTA review bodies have varying levels of familiarity and confidence in PRO data
 - Different types of PRO data creates difficulty in understanding measures and assigning value¹
 - Payers often mistakenly consider PRO to be synonymous with QoL¹
 - Low use of outcomes data in the US due to unsatisfactory quality and quantity of data²
- Most payers are unfamiliar with the specifics of FDA PRO Guidance document²
- Label claims related to HRQoL are more frequent in EMA labels than FDA labels

¹Zagadailov E, Fine M, Shields A. Patient-reported outcomes are changing the landscape in oncology care: challenges and opportunities for payers. Am Health Drug Benefits. 2013;6(5):264-274

²Svodoba K, White N. Payer evidence requirements for new drugs: trends and impact. Academy of Managed Care Pharmacy, Spring 2014. Available at: <http://www.ajmc.com/conferences/AMCPSpring2014/Payer-Evidence-Requirements-for-New-Drugs-Trends-and-Impact>. Accessed July 20, 2014.

PRO Data Is Considered by Most Major Market Payer Decision Makers



- PRO evidence is generally thought to be **complimentary** to clinical and safety endpoints.
- There are minimal requirements or guidelines specifically addressing whether and how **payer decision makers** use PRO evidence.
- PRO evidence is typically evaluated on a **case-by-case basis**, and the quality of the PRO evidence is paramount to consideration.

"PRO data [are] considered. Needs to be patient relevant, improvements in morbidity, side effects, QOL.

Compliance and convenience are not considered."



—Germany Payer Advisor

"PRO can move the needle. Really need to publish and educate payers about PROs outside of QALYs."

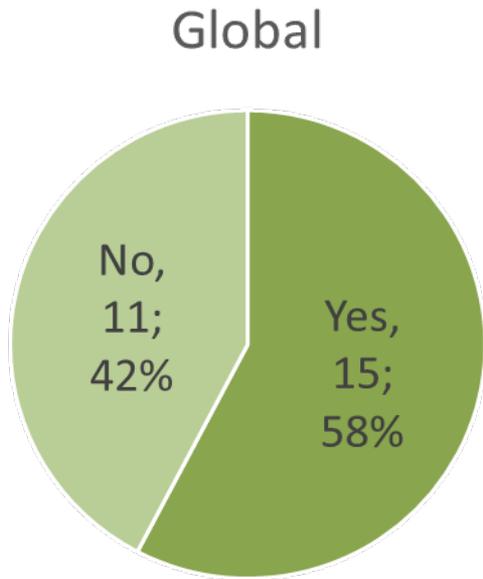
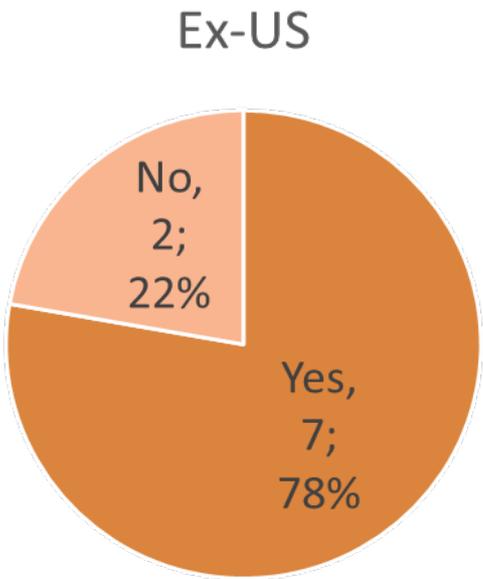
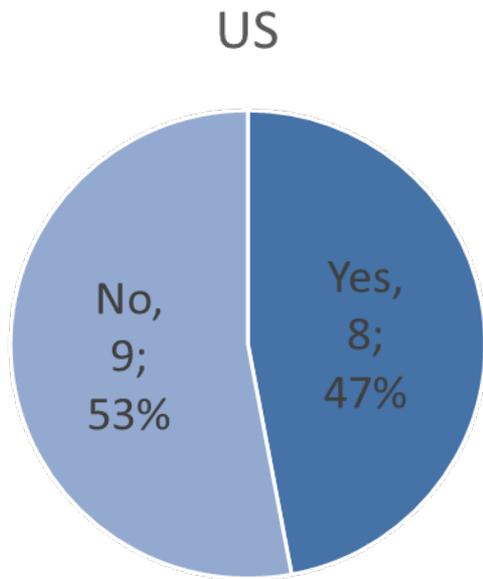


—South Korea Payer Advisor

PRO Data: Mixed Impact in US; Greater Impact Ex-US



Survey Question: Does PRO data impact decision making when considering one therapy over another?



Examples Where PRO Data Impacted Payer Decision Making



- Survey Question: Are you aware of examples of oncology products that received favorable reimbursement decisions because of PRO data?
 - In US health plans: Enzalutamide for prostate cancer and ruxolitinib for myelofibrosis.
- PRO data were critical for crizotinib to achieve an additional benefit rating under AMNOG.
 - Additional benefit assignment is crucial to achieving any price premium in Germany.
 - This finding is consistent with the literature review findings.

“For crizotinib, PRO data [were] a 7 [highest impact rating]. Additional benefit based on PRO data on symptoms and QOL (EORTC scale). No additional benefit based on mortality.”



—Germany Payer Advisor

Impact of PRO Data varies by Therapeutic Area



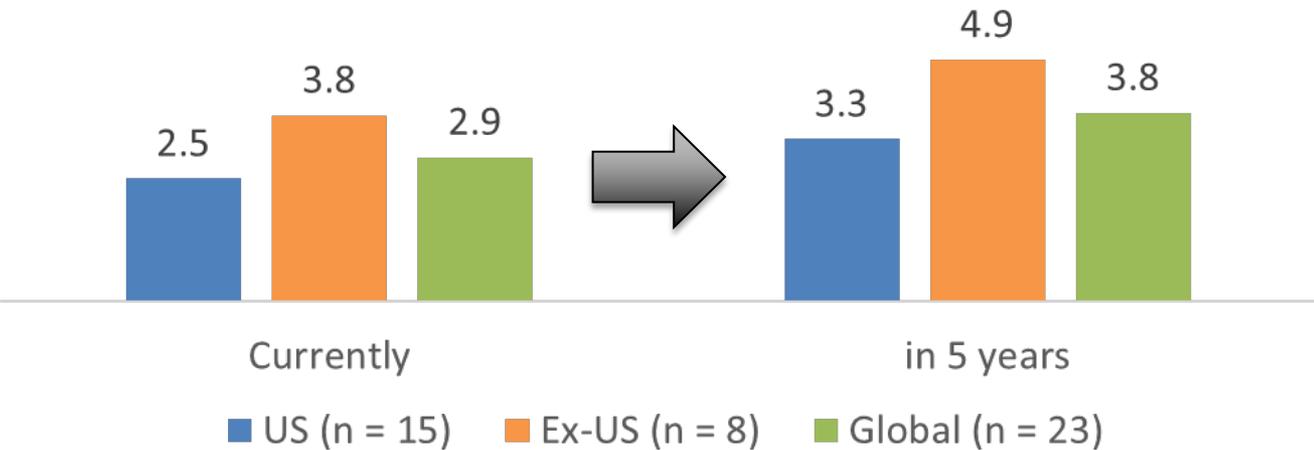
- Payers ranked the following disease areas in terms of impact of PRO information on influencing decision making for one therapy or another:
 1. Oncology
 2. (Tie) CNS: Neurology and neurodegenerative
CNS: Psychiatry
 3. (Tie) Diabetes/metabolic disease
Autoimmune disorders
 4. Lifestyle (e.g., obesity, smoking)

N = 12 (7 US, 5 Ex-US)

PRO Data Expected to Increase in Importance Over the next 5-10 Years and Could be a Key Differentiator



- Survey Question: Payers were asked to rate the importance of PRO data for market access for new oncology treatments currently and estimated importance in 5 years on a scale of 1 to 7, where 1 means “not important” and 7 means “extremely important.”



“We consider PRO data now, but [they don’t] impact things too much directly. But I am expecting it to have a bigger impact in the future, especially when/if we start considering value more.”

—US Medical Director

“Five years from now, I hope it is [a rating of] 4-5; 10 years from now, I hope it is a 7. I'd rather have robust PRO data than an extra 3 weeks in oncology, but [the system] is just not there yet.”

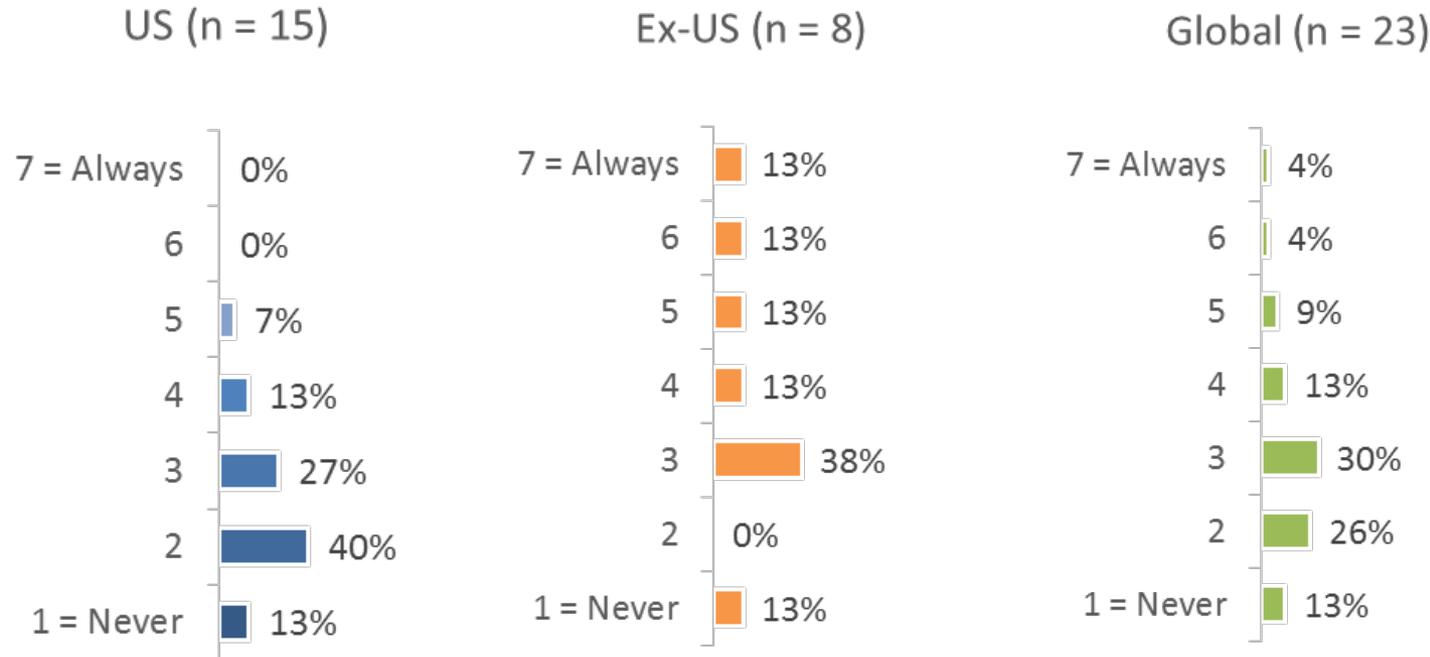
—US Medical Director

Influence of PRO Label Claim on Payer Decision Making



- Currently, PRO label claims have more of an influence on paying for a treatment outside the US.
- US payer decision making in the future may be impacted through increased awareness and education of PRO label claims

Survey Question: To what extent do PRO label claims increase your likelihood of paying for a treatment?

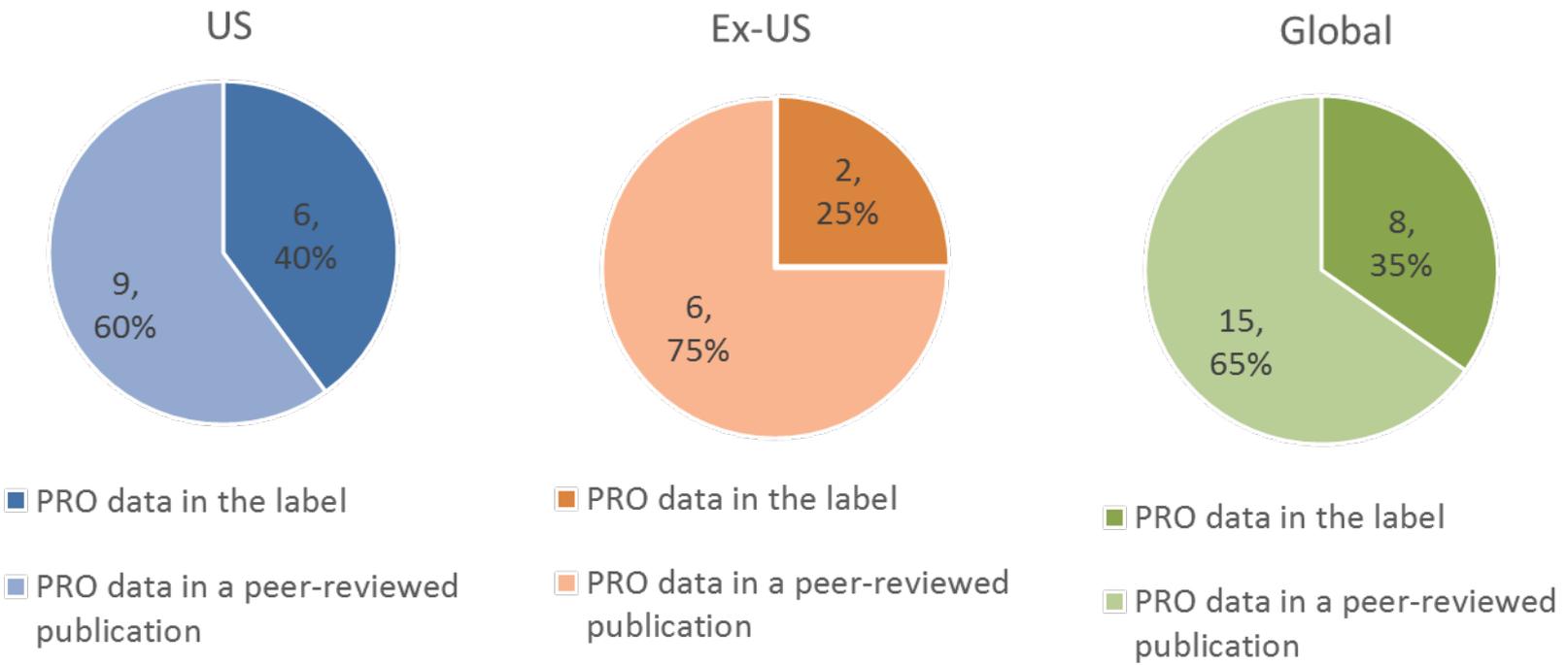


Published PRO Data is More Important than Label Claim



- Peer-reviewed publications of PRO data are critical for impact on payer decision-making

Survey Question: Which has more impact on decision making for a new treatment, PRO data in the label or PRO data in a peer-reviewed publication?



PRO scale validation most important trait in payer decision making

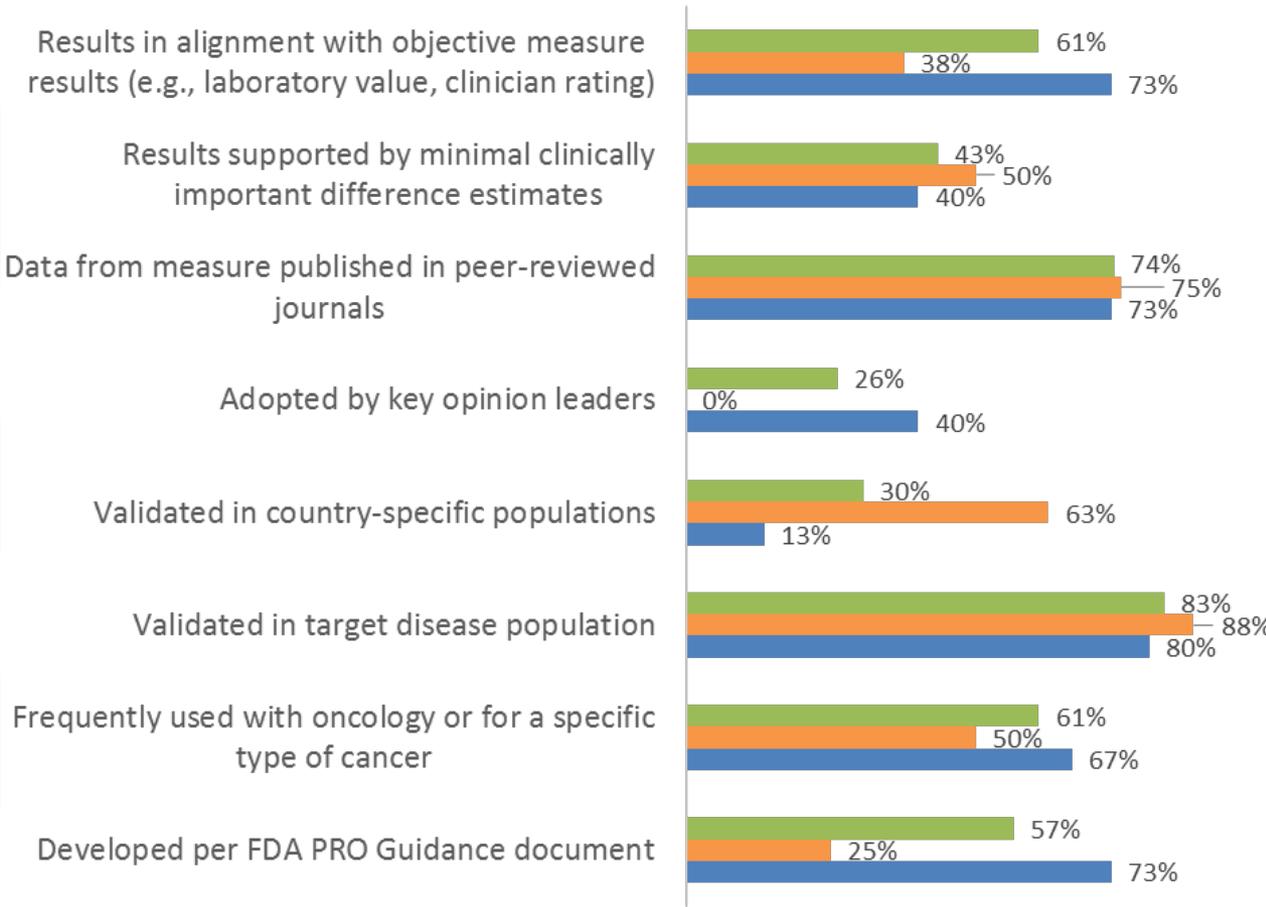


Survey Question: What characteristics should a PRO measure for a treatment in oncology have in order to support market access and HTA? Select all that apply.

Payers value if scale is validated in target disease populations and data from the measure is published in peer-reviewed journal.

US Payers also value if scale is developed per FDA PRO guidance, however most payers are unfamiliar with guidance.

Ex-US Payers also value if the scale is validated in country specific populations



■ Global (n = 23) ■ Ex-US (n = 8) ■ US (n = 15)

Industry Needs to Educate Payers and Prescribers on the Value of PRO Data

[PRO data should:]

“Demonstrate patient-relevant benefit
Use validated, existing instruments
Compare to appropriate comparator (as determined by G-Ba)”



—Germany Payer Advisor

“[Manufacturers should] integrate PRO data with clinical outcomes as part of the broader value proposition and to make that very clear as a potential differentiator relative to other products.”



—US Medical Director

“This is the flow of information:

Manufacturer » clinician » reimbursement authority.”



—Netherlands Payer Advisor

“The prescribers are not used to PRO data and they need to be educated. They focus more on tumour progression and progression-free survival.”



—Sweden Payer Advisor

Key Learnings

- PRO data are growing in importance in payer decision making
- Validation in target disease populations and publications in peer-reviewed journals are key to influencing payer decision making
- PRO data need to be tied to the bigger value story for new treatments

Key Takeaways

- Manufacturers need to incorporate PRO measures in registration trials and postmarketing studies in order to impact payer decision making
- Validation and publication of a PRO measure is critical for consideration in payer decision making
- Manufacturers should educate payers on the PRO data pertinent to their therapy and tie it to the broader value story for new therapies introduced to the market

Katarina Halling, MSC
Patient Reported Outcomes Group Director
AstraZeneca

***SIXTH ANNUAL
PATIENT-REPORTED OUTCOME CONSORTIUM WORKSHOP***

April 29 - 30, 2015 ■ Silver Spring, MD

Discussion and/or Questions?

Moderator

- Peter C. Trask, Ph.D., MPH, Principal PCOR Scientist, Genentech

Presenters and Panelists

- David S. Reasner, PhD – Vice President, Data Science & Head, Study Endpoints, Ironwood Pharmaceuticals
- Vasudha Bal, MSc, MBA – Director, PRO, Novartis Pharmaceuticals
- Katarina Halling, MSc – PRO Group Director, AstraZeneca
- Robin S. Turpin, PhD – Director and Head, U.S. HEOR, U.S. Medical and Scientific Affairs, Takeda Pharmaceuticals
- Alan L. Shields, PhD – Vice President, Endpoint Development and Outcomes Assessment, Adelphi Values
- Selena Daniels, PharmD, MS – Study Endpoints Reviewer, Study Endpoints and Labeling Development, FDA