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When Does Mode of Data Collection Matter? Updated and Expanded Recommendations for Collecting PRO Measures Electronically in Clinical Trials

presented by the ISPOR Measurement Comparability of PROMs Good Practices Task Force

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via the chat box.

We will address comments in the discussion session *after* the presentations.

Moderator:

Paul O'Donohoe, MSc, **Co-Chair**; Scientific Lead, eCOA and Mobile Health, Medidata, London, England, UK

Speakers:

- **Sonya Eremenco, MA,** Acting Director, Electronic Patient-Reported Outcome (ePRO) Consortium, and Associate Director, Patient-Reported Outcome (PRO) Consortium, Critical Path Institute, Tucson, AZ, USA
- **David Reasner, PhD, Co-Chair**; President and Founder, Albemarle Scientific Consulting, Moultonborough, NH, USA
- **Sarrit Kovacs, PhD,** Clinical Reviewer, Division of Gastroenterology, Office of Immunology and Inflammation, Office of New Drugs, Center for Drug Evaluation and Research (CDER), US Food and Drug Administration (FDA), Silver Spring, MD, USA *(formerly Team Leader in the Division of Clinical Outcome Assessment [DCOA])*

Task Force Members

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- **Alexandra I Barsdorf, PhD,** Director, Clinical Outcomes Solutions, New York, NY, USA
- **Serge Bodart, MSc**, Chief Commercial Officer (CCO) at IDDI and Independent eCOA Subject Matter Expert, Brussels, Belgium
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- **Stephen Joel Coons, PhD**, Executive Director, PRO Consortium and Program Officer, COA Program, Critical Path Institute, Tucson, AZ, USA
- **Jean Paty, PhD,** Vice President, Patient-Centered Endpoints, Real-World and Analytic Solutions, QuintilesIMS, New York, NY, USA
- **Megan Turner, BA,** Scientist, COA Implementation, GSK, Collegeville, PA, USA
- **Sue Vallow**, MBA, MA, RPh, Executive Director, Patient-Centered Outcomes / PCO Lead, Global Value and Access, Novartis Oncology, East Hanover, NJ, USA

ISPOR's 12 PRO/COA Good Practices Task Force Reports* - 1

1. Translation and Linguistic Validation of PRO Instruments (2005†; 2009)
2. Measurement Equivalence Between Electronic and Paper-Based PRO Measures (2009)
3. Content Validity in Existing PRO Instruments and Their Modification (2009)
4. Content Validity in Newly Developed PRO Instruments Part 1 – Eliciting Concepts for a New PRO Instrument (2011)
5. Content Validity in Newly-Developed PRO Instruments Part 2 – Assessing Respondent Understanding (2011)
6. ePRO Systems Validation (2013)
7. Assessment of PROs in Children and Adolescents (2013)

**Based on FDA's PRO Guidance for Industry, 2009*

† Landmark methodology report

ISPOR's 11 PRO/COA Good Practices Task Force Reports - 2

8. Mixed Modes to Collect PRO Data in Clinical Trials (2014)
9. Clinical Outcome Assessments: A Conceptual Foundation (2015)
10. Clinician-Reported Outcomes (ClinROs) Good Measurement Practices (2017)
11. PRO and Observer Reported Outcomes (ObsRO) Assessment in Rare Disease Clinical Trials (2017)

- Measurement Comparability of PROMs (*in development; 2021*)
- Performance-based Outcomes Assessments – Part 1: Introduction (*in development; 2021*)
- Performance-based Outcomes Assessments – Part 2: Emerging Good Practices (*upcoming*)

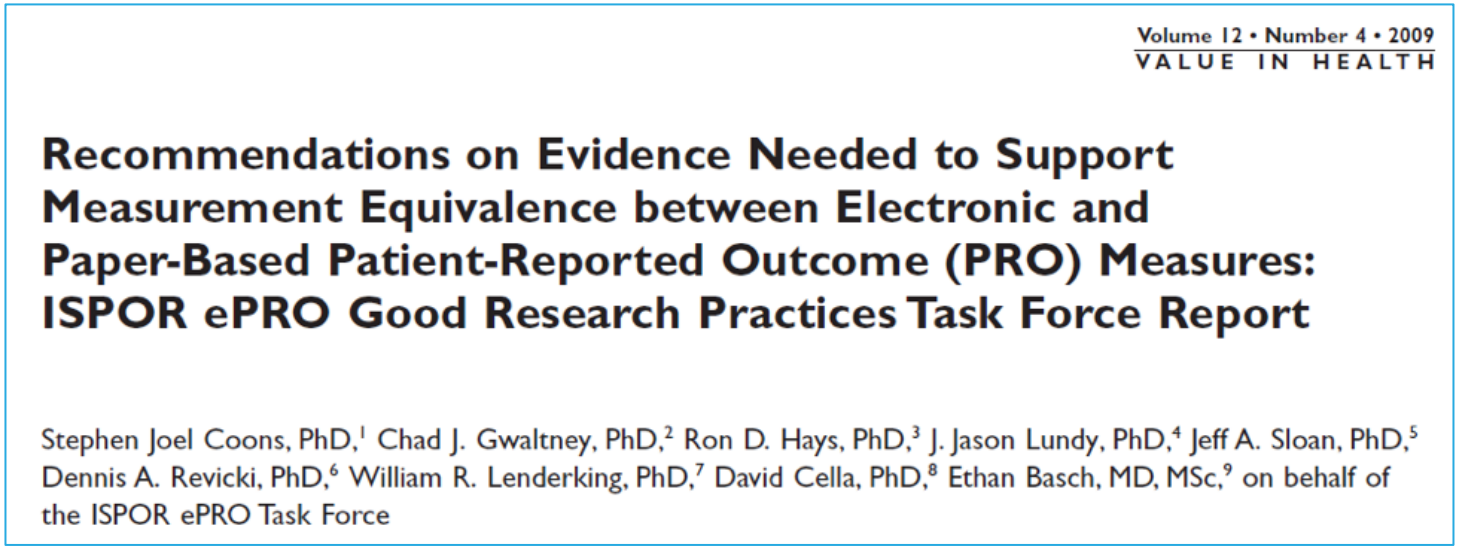
SECTION

1

Background

- *Paul O'Donohoe, Medidata*

Task Force Updating Two Reports: 1



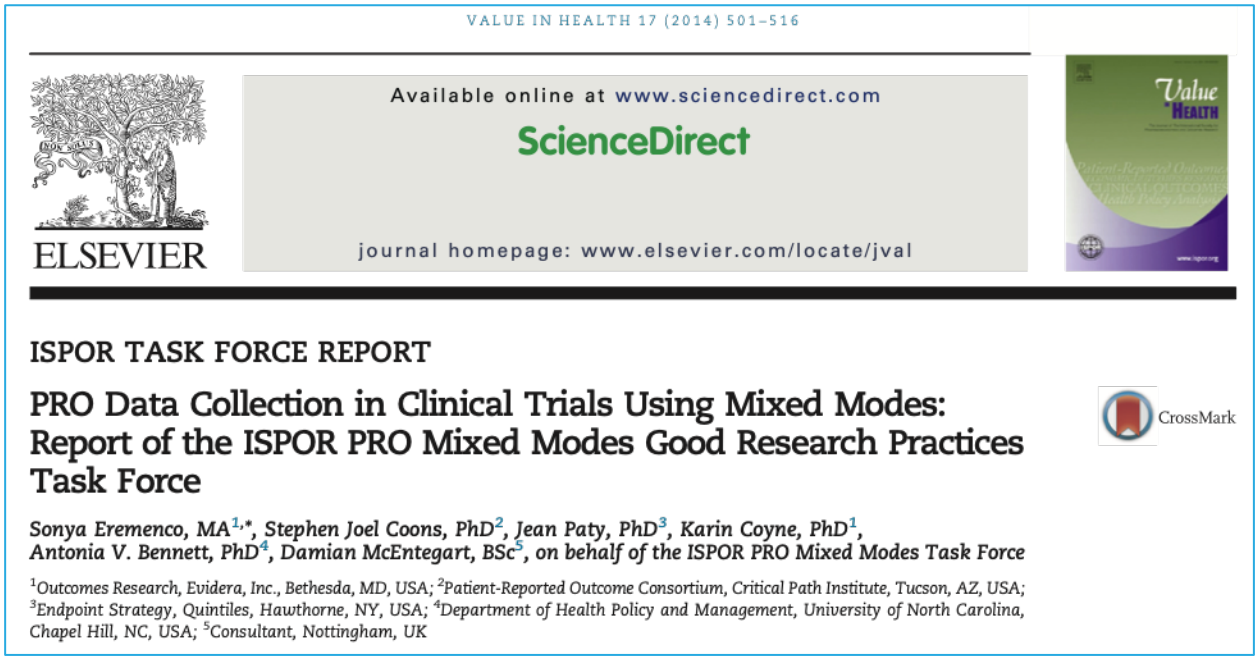
Volume 12 • Number 4 • 2009
VALUE IN HEALTH

Recommendations on Evidence Needed to Support Measurement Equivalence between Electronic and Paper-Based Patient-Reported Outcome (PRO) Measures: ISPOR ePRO Good Research Practices Task Force Report

Stephen Joel Coons, PhD,[1] Chad J. Gwaltney, PhD,[2] Ron D. Hays, PhD,[3] J. Jason Lundy, PhD,[4] Jeff A. Sloan, PhD,[5] Dennis A. Revicki, PhD,[6] William R. Lenderking, PhD,[7] David Cella, PhD,[8] Ethan Basch, MD, MSc,[9] on behalf of the ISPOR ePRO Task Force

Coons SJ, Gwaltney CJ, Hays RD, et al. Recommendations on evidence needed to support measurement equivalence between electronic and paper-based patient-reported outcome (PRO) measures: ISPOR ePRO Good Research Practices Task Force Report. *Value Health*. 2009;12:419–29.

Task Force Updating Two Reports: 2



VALUE IN HEALTH 17 (2014) 501–516

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ISPOR TASK FORCE REPORT

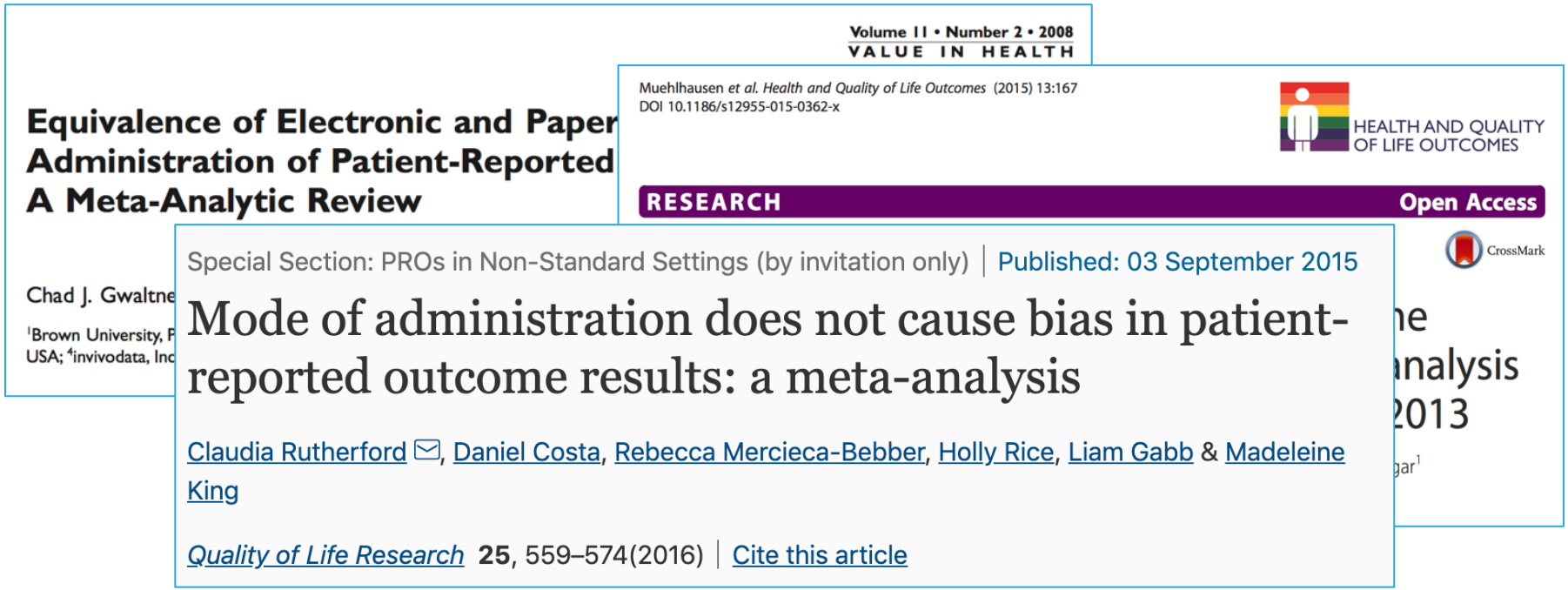
PRO Data Collection in Clinical Trials Using Mixed Modes: Report of the ISPOR PRO Mixed Modes Good Research Practices Task Force

Sonya Eremenco, MA[1,], Stephen Joel Coons, PhD[2], Jean Paty, PhD[3], Karin Coyne, PhD[1], Antonia V. Bennett, PhD[4], Damian McEntegart, BSc[5], on behalf of the ISPOR PRO Mixed Modes Task Force*

[1]*Outcomes Research, Evidera, Inc., Bethesda, MD, USA;* [2]*Patient-Reported Outcome Consortium, Critical Path Institute, Tucson, AZ, USA;* [3]*Endpoint Strategy, Quintiles, Hawthorne, NY, USA;* [4]*Department of Health Policy and Management, University of North Carolina, Chapel Hill, NC, USA;* [5]*Consultant, Nottingham, UK*

Eremenco S, Coons SJ, Paty J, et al. PRO data collection in clinical trials using mixed modes: report of the ISPOR PRO mixed modes good research practices task force. *Value Health*. 2014;17:501–16.

Accumulating Evidence of Comparability



Summary

- Muehlhausen et al. largely representative of the evidence: "*results…indicate that electronic and paper PROMs and different modes of electronic administration produce equivalent scores across a wide range of scenarios (medical conditions and platforms), suggesting that electronic measures can generally be assumed to be equivalent to pen and paper measures*"

- Gwaltney CJ, Shields AL, Shiffman S. Equivalence of electronic and paper- and pencil administration of patient reported outcome measures: a meta-analytic view. *Value Health*. 2008;11:322–33.
- Muehlhausen W, Doll H, Quadri N, et al. Equivalence of electronic and paper administration of patient-reported outcome measures: a systematic review and meta-analysis of studies conducted between 2007 and 2013. *Health Qual Life Outcomes*. 2015;13:167.
- Rutherford C, Costa D, Mercieca-Bebber R, Rice H, Gabb L, King M. Mode of administration does not cause bias in patient-reported outcome results: a meta-analysis. *Qual Life Res*. 2016;(3):559-74.

2

Existing Good Practice Recommendations

- Sonya Eremenco, Critical Path Institute

Brief history of migration/equivalence recommendations

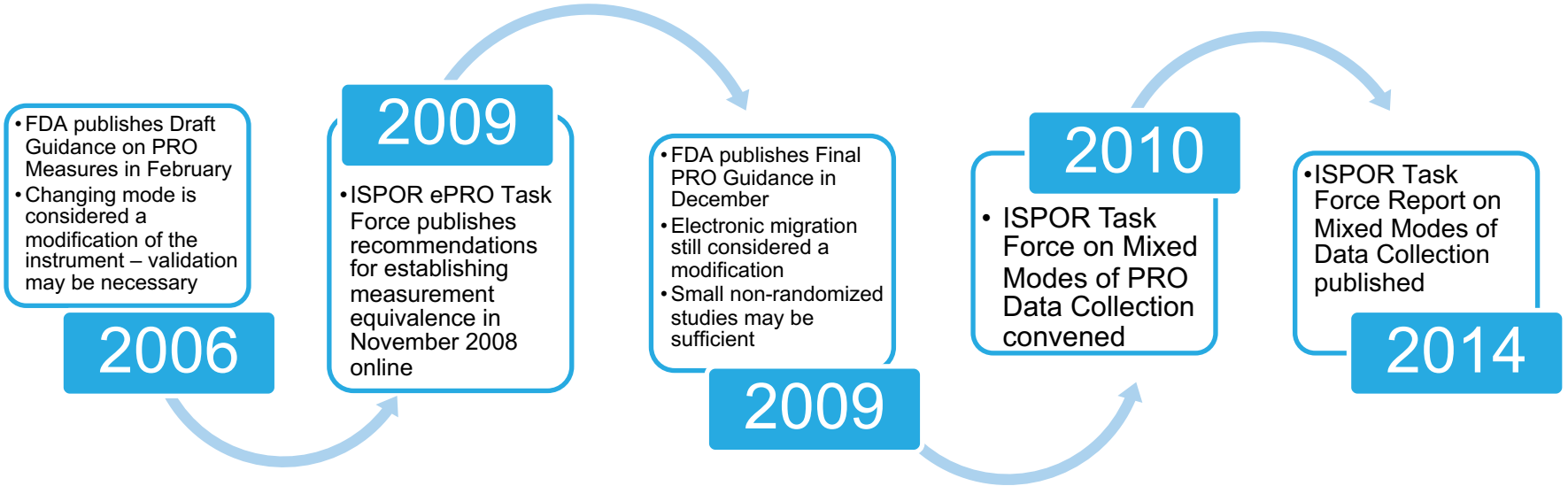


Table 1, Coons 2009

Table 1 PRO to ePRO measurement equivalence: instrument modification and supporting evidence

Level of modification	Rationale	Examples	Level of evidence
Minor	The modification can be justified on the basis of logic and/or existing literature. No change in content or meaning.	1) Nonsubstantive changes in instructions (e.g., from circling the response to touching the response on a screen). 2) Minor changes in format (e.g., one item per screen rather than multiple items on a page).	Cognitive debriefing Usability testing
Moderate	Based on the current empirical literature, the modification cannot be justified as minor. May change content or meaning.	1) Changes in item wording or more significant changes in presentation that might alter interpretability. 2) Change in mode of administration involving different cognitive processes (e.g., paper [visual] to IVR [aural]).	Equivalence testing Usability testing
Substantial	There is no existing empirical support for the equivalence of the modification and the modification clearly changes content or meaning	1) Substantial changes in item response options 2) Substantial changes in item wording	Full psychometric testing Usability testing

Adapted from Shields et al. [62].

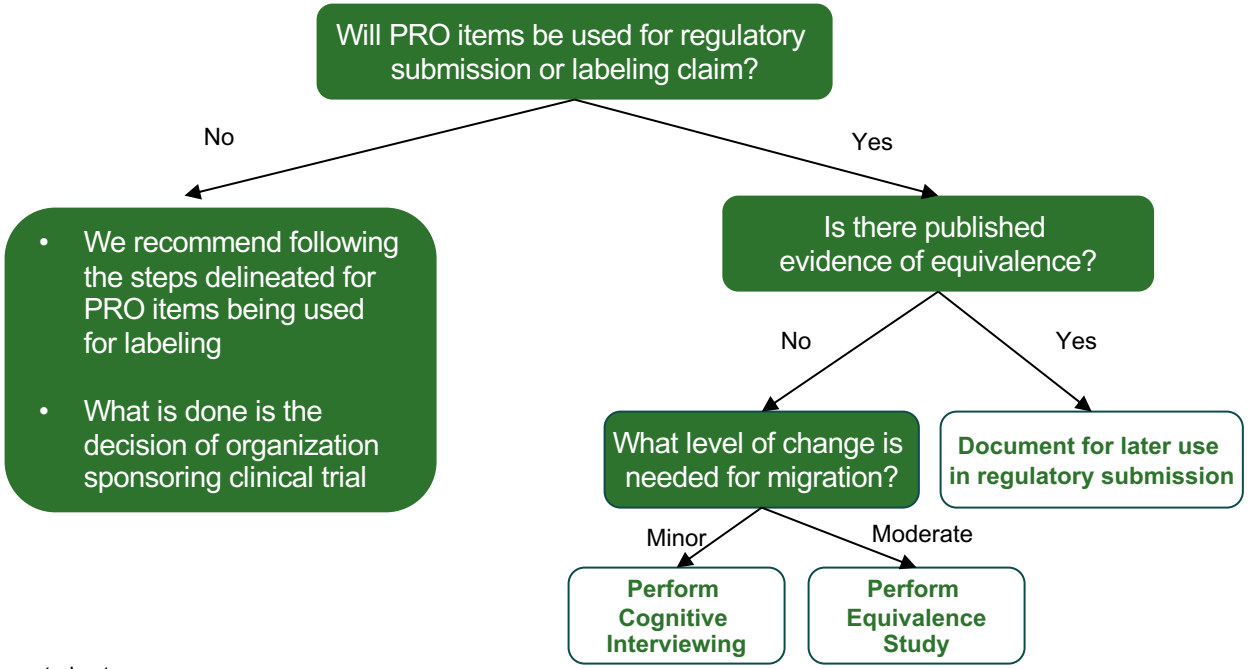
Coons SJ, Gwaltney CJ, Hays RD, et al. Recommendations on evidence needed to support measurement equivalence between electronic and paper-based patient-reported outcome (PRO) measures: ISPOR ePRO Good Research Practices Task Force Report. *Value Health.* 2009;12(4):419-429.

ISPOR Mixed Modes Task Force Recommendations

1. Select appropriate mode(s) for trial
2. Perform a “faithful migration” (“migrate before you mix”)
   - Only necessary changes to the format and instructions are made and that the content of the items and responses has not changed.
   - Subjects ***interpret and respond*** to the questions/items the same way regardless of mode
3. Evaluate equivalence between the modes migrated and/or to be mixed
   - Use appropriate study design
4. If above conditions are met, implement the mode or modes in the trial
   - Avoid mixing paper and electronic diaries; assess risks of other combinations
   - If deciding to mix other modes
     - Plan and implement carefully; mix at country level or higher
     - Assess statistical issues and poolability of data

Eremenco S, Coons SJ, Paty J, et al. PRO data collection in clinical trials using mixed modes: report of the ISPOR PRO mixed modes good research practices task force. *Value Health*. 2014;17(5):501-516.

Original: Need to Establish Measurement Equivalence



PRO, patient-reported outcome

Additional Literature on Equivalence/Comparability

- EuroQol 5-Dimension questionnaire (EQ-5D): IVR and Paper
  - Lundy JJ, Coons SJ. Measurement equivalence of interactive voice response and paper versions of the EQ-5D in a cancer patient sample. *Value Health*. 2011;14(6):867-871.
- EORTC: IVR and Paper
  - Lundy JJ, Coons SJ, Aaronson NK. Testing the measurement equivalence of paper and interactive voice response system versions of the EORTC QLQ-C30. *Qual Life Res*. 2014;23(1):229-237.
- PROMIS Physical Function, Fatigue, Depression banks: personal computer (PC) vs. IVR, personal digital assistant (PDA), Paper, or PC
  - Bjorner JB, Rose M, Gandek B, et al. Method of administration of PROMIS scales did not significantly impact score level, reliability, or validity. *J Clin Epidemiol*. 2014;67(1):108-113.
- Reviews of paper vs. electronic studies
  - Campbell N, Ali F, Finlay AY, Salek SS. Equivalence of electronic and paper-based patient-reported outcome measures. *Qual Life Res*. 2015;24(8):1949-1961.
  - Rutherford, C., Costa, D., Mercieca-Bebber, R., Rice, H., Gabb, L. & King, M. Mode of administration does not cause bias in patient-reported outcome results: a meta-analysis. *Quality of Life Research*. 2016 Mar;25(3):559-74.
- Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE): Web, IVR and Paper
  - Bennett AV, Dueck AC, Mitchell SA, et al. *Health Qual Life Outcomes.* 2016; **14**:24. https://doi.org/10.1186/s12955-016-0426-6
- Bowel function instrument, linear analog scale assessment (LASA) quality-of-life (QOL) and Adapted Sydney Swallow Questionnaire (SSQ): Web, IVR and Paper
  - Bennett AV, Keenoy K, Shouery M, et al. *Qual Life Res*. 2016 May;25(5):1123-30. doi: 10.1007/s11136-015-1162-9.
- Bring your own device (BYOD)
  - Coons SJ, Eremenco S, Lundy JJ, et al. Capturing Patient-Reported Outcome (PRO) Data Electronically: The Past, Present, and Promise of ePRO Measurement in Clinical Trials. *Patient*. 2015;8(4):301-309.
  - Gwaltney C, Coons SJ, O'Donohoe P, O'Gorman H, Denomey M, Howry C, Ross J. "Bring Your Own Device" (BYOD): The future of field-based patient-reported outcome data collection in clinical trials? *Ther Innov Regul Sci.* 2015 Nov;49(6):783-791. doi: 10.1177/2168479015609104.

Preliminary Updated Recommendations

- *David Reasner, Albemarle Scientific Consulting*

High Level Update

- Terminology - “Comparability” preferred over “Equivalence”
- **There is enough evidence that, in many instances, additional equivalence testing is no longer necessary**
- Comparability relies on “eCOA design best practices”
  - ePRO Consortium white papers
  - Eremenco 2014
  - Oxford University Innovations white paper
- The goal is not to be prescriptive, but rather to empower readers to be able to make a reasoned assessment on a case-by-case basis, keeping in mind future technologies and research

Proposed Update to “Levels of Change”

- Shift the focus from the amount of change that’s occurred during migration to **whether there is sufficient supporting evidence for that change**
- Merging Minor and Moderate to…**Minor/Moderate**
- Different instruments and target technologies introduce a range of changes which, considered in isolation, might be minor or moderate, but when taken as a whole fall somewhere between the two – **a spectrum**
- **Substantial** levels of change remains much the same – dealing with new items or a new instrument

Levels of Existing Evidence

- One should assess whether there is **Sufficient** evidence suggesting the migration has not impacted how patients are interpreting and responding (maintained comparability)

- If **Insufficient** evidence, additional research might be appropriate

“Sufficient” Evidence

- The existing literature supports the assumption that the change which has occurred during the migration process is unlikely to have impacted the comparability of the instrument between/across modes
  - Also includes unpublished reports and grey literature
- Does **not** have to be evidence of the exact instrument – “similar instruments composed of the same types of response scales”
- “Sufficient” evidence is:
  - targeted or relevant to the question
  - supports the assumption of comparability
  - unbiased and balanced research
  - the preponderance of available evidence points to the same conclusion

If “Insufficient” Evidence

- Existing literature (including unpublished reports and grey literature) does not provide enough evidence to support the assumption that the change which has occurred during the migration process has not impacted the comparability of the instrument between/across modes
- Additional research may range from cognitive interviewing and usability testing, to quantitative comparability testing, depending on the specifics of the instrument and its use
- More generally, perform qualitative and/or quantitative research to assess understanding, and a psychometric evaluation, as needed, employing established or, increasingly, innovative methods

Table 1, Coons 2009

Table 1 PRO to ePRO measurement equivalence: instrument modification and supporting evidence

Level of modification	Rationale	Examples	Level of evidence
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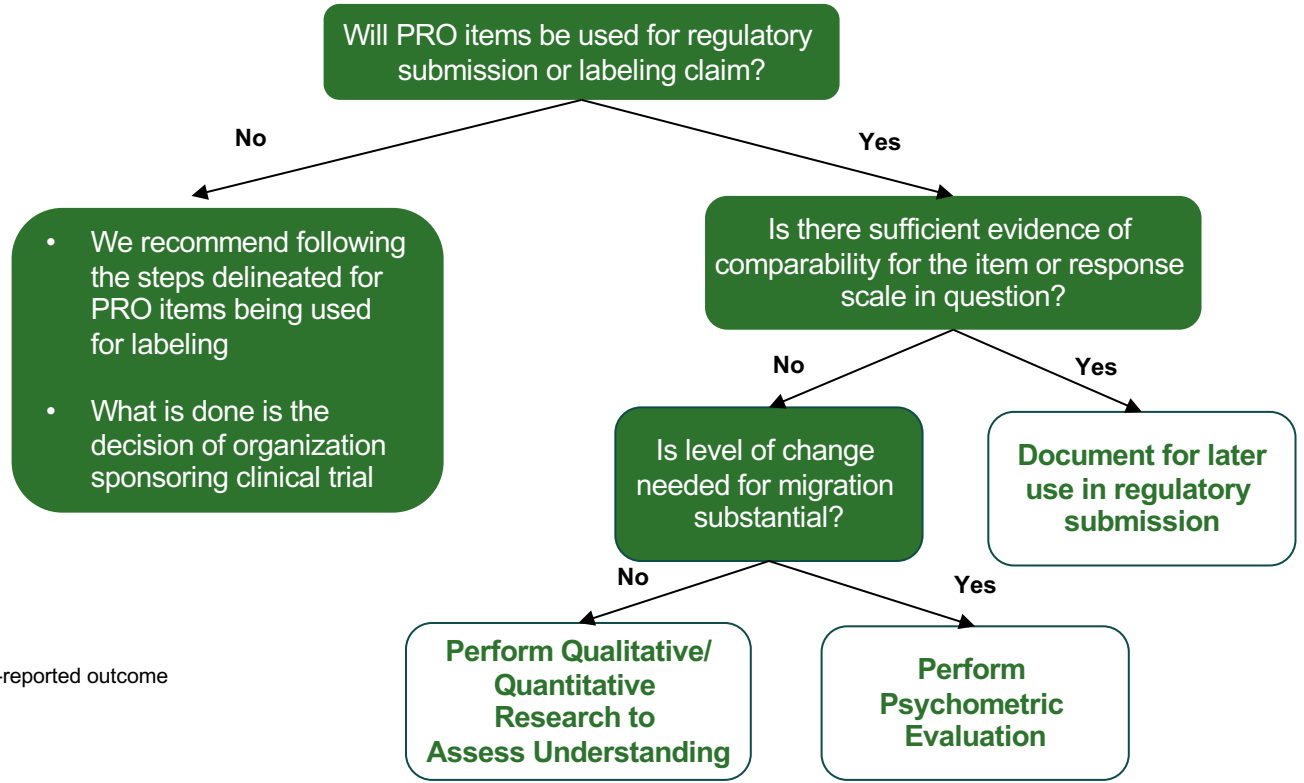
Adapted from Shields et al. [62].

ISPOR Comparability of PROMs Task Force: Proposed New Table

		Levels of Change	
		Minor/Moderate	**Substantial**
Existing Evidence	**Sufficient**	• Summary of the existing evidence • Demonstration of following design best practice	• Summary of the existing evidence • Demonstration of following design best practice
	Insufficient	A range from cognitive interviewing and usability testing, to quantitative comparability testing, depending on the specifics of the instrument and the changes introduced during migration	Full psychometric evaluation/analysis

Revised: Need to Establish Measurement Comparability



PRO, patient-reported outcome

4

Regulatory Perspective (FDA)

- Sarrit Kovacs, FDA

Speaker Disclaimer

- The views expressed in this presentation are those of the speaker, and do not necessarily represent an official FDA position.

Advantages of Migration to Electronic Data Capture (EDC)

- Less risk of data error (less human error)
- Direct transmission of electronic data may reduce risk to data integrity
- Less risk of missing data
- Potential for greater patient compliance (alarms, date/time stamps)

FDA Review of ePRO Data

- Documentation of development and validation of electronic PROs (ePROs) may be important to review
  - design features, usability testing, training materials/device usage instructions, ePRO standardization and comparability across platforms, etc.
- FDA's PRO Guidance describes good measurement principles for developing PRO instruments; some applicable to other COA types
  - Provides an optimal approach, but flexibility & judgment are necessary

ePRO Data: Data-related Regulatory Issues

- Sponsors and investigators must ensure that electronic records and electronic signatures used in clinical investigations meet FDA regulatory requirements for record keeping, maintenance, and access (21 CFR Part 11)
- These responsibilities include:
  - Establishing appropriate system and security controls
  - Establishing database backup procedures
  - Taking steps to avoid premature or unplanned access to unblinded data
- The clinical trial protocol (or another document) should specify how the ePRO source data will be maintained and how the investigator will meet the regulatory requirements.

FDA Regulatory Standards, and Other EDC Guidelines

- 21 CFR Part 11 “Electronic Records; Electronic Signatures”
  - http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?fr=11.10
  - eCFR: http://www.ecfr.gov/cgi-bin/text-idx?SID=3ee286332416f26a91d9e6d786a604ab&mc=true&tpl=/ecfrbrowse/Title21/21tab_02.tpl
- 21 CFR Parts 312 (drugs) and 812 (devices)
  - http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?CFRPart=312
- ICH Guideline for Good Clinical Practice E6 (R1) - Section 5.5.3
  - http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R1_Guideline.pdf

Available FDA Guidance for Industry on EDC

- Guidance for Industry: Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims (December 2009)
  - http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071975.pdf
- Guidance for Industry: Part 11 - Electronic Records: Electronic Signatures (August 2003)
  - http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm125125.pdf
- Guidance for Industry: Computerized Systems Used in Clinical Investigations (May 2007)
  - http://www.fda.gov/OHRMS/DOCKETS/98fr/04d-0440-gdl0002.pdf
- Guidance for Industry: Electronic Source Data in Clinical Investigations (September 2013)
  - http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm328691.pdf

The latter three guidance documents are to be used together

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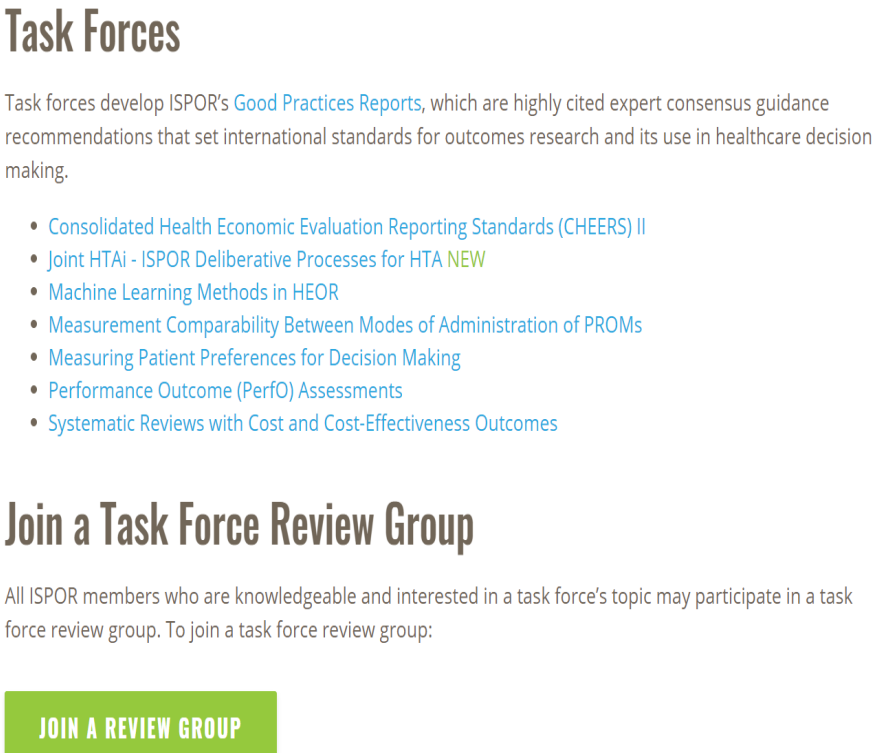

Task Forces

Task forces develop ISPOR’s Good Practices Reports, which are highly cited expert consensus guidance recommendations that set international standards for outcomes research and its use in healthcare decision making.

- Consolidated Health Economic Evaluation Reporting Standards (CHEERS) II
- Joint HTAi - ISPOR Deliberative Processes for HTA NEW
- Machine Learning Methods in HEOR
- Measurement Comparability Between Modes of Administration of PROMs
- Measuring Patient Preferences for Decision Making
- Performance Outcome (PerfO) Assessments
- Systematic Reviews with Cost and Cost-Effectiveness Outcomes

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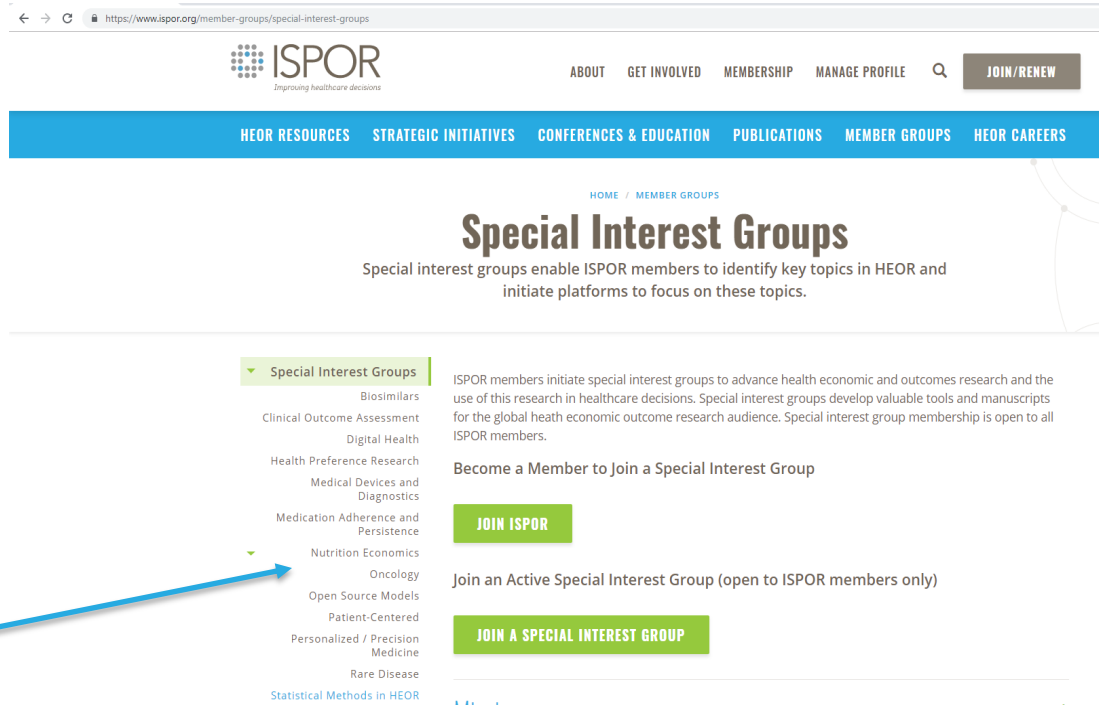

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Discussion

Please feel free to email any follow-up questions or comments to podonohoe@medidata.com