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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We will address comments in the discussion session after the presentations.
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Speakers:
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• 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])
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• **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)
3. Content Validity in Existing PRO Instruments and Their Modification (2009)
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)
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*)
Background

- Paul O’Donohoe, Medidata
Task Force Updating Two Reports: 2

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, MA1, *, Stephen Joel Coons, PhD2, Jean Paty, PhD3, Karin Coyne, PhD1, Antonia V. Bennett, PhD3, Damian McEntegart, BSc3, on behalf of the ISPOR PRO Mixed Modes Task Force

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

Accumulating Evidence of Comparability

Equivalence of Electronic and Paper Administration of Patient-Reported A Meta-Analytic Review

Chad J. Gwaltney
1Brown University, Providence, RI, USA; 2invivodata, Inc., Providence, RI, USA

Special Section: PROs in Non-Standard Settings (by invitation only)  Published: 03 September 2015

Mode of administration does not cause bias in patient-reported outcome results: a meta-analysis

Claudia Rutherford, Daniel Costa, Rebecca Mercieca-Bebber, Holly Rice, Liam Gabb & Madeleine King

Quality of Life Research  25, 559–574(2016)  Cite this article
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”

Existing Good Practice Recommendations
- Sonya Eremenco, Critical Path Institute
Brief history of migration/equivalence recommendations

2006
- FDA publishes Draft Guidance on PRO Measures in February
- Changing mode is considered a modification of the instrument – validation may be necessary

2009
- ISPOR ePRO Task Force publishes recommendations for establishing measurement equivalence in November 2008 online
- FDA publishes Final PRO Guidance in December
- Electronic migration still considered a modification
- Small non-randomized studies may be sufficient

2010
- ISPOR Task Force on Mixed Modes of PRO Data Collection convened
- ISPOR Task Force Report on Mixed Modes of Data Collection published

2014
Table 1, Coons 2009

<table>
<thead>
<tr>
<th>Level of modification</th>
<th>Rationale</th>
<th>Examples</th>
<th>Level of evidence</th>
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Adapted from Shields et al. [62].
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

Original: Need to Establish Measurement Equivalence

Will PRO items be used for regulatory submission or labeling claim?

Yes

Is there published evidence of equivalence?

No

What level of change is needed for migration?

No

Document for later use in regulatory submission

Yes

Minor

Perform Cognitive Interviewing

Moderate

Perform Equivalence Study

• We recommend following the steps delineated for PRO items being used for labeling
• What is done is the decision of organization sponsoring clinical trial

PRO, patient-reported outcome
Additional Literature on Equivalence/Comparability

- EuroQol 5-Dimension questionnaire (EQ-5D): IVR and Paper

- EORTC: IVR and Paper

- PROMIS Physical Function, Fatigue, Depression banks: personal computer (PC) vs. IVR, personal digital assistant (PDA), Paper, or PC

- Reviews of paper vs. electronic studies

- Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE): Web, IVR and Paper

- Bowel function instrument, linear analog scale assessment (LASA) quality-of-life (QOL) and Adapted Sydney Swallow Questionnaire (SSQ): Web, IVR and Paper

- Bring your own device (BYOD)
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
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## ISPOR Comparability of PROMs Task Force: Proposed New Table

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**Existing Evidence**
Revised: Need to Establish Measurement Comparability

Will PRO items be used for regulatory submission or labeling claim?

- No
  - We recommend following the steps delineated for PRO items being used for labeling
  - What is done is the decision of organization sponsoring clinical trial

- Yes
  - Is there sufficient evidence of comparability for the item or response scale in question?
    - No
      - Is level of change needed for migration substantial?
        - No
          - Perform Qualitative/Quantitative Research to Assess Understanding
        - Yes
          - Perform Psychometric Evaluation
    - Yes
      - Document for later use in regulatory submission

PRO, patient-reported outcome
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”
  – 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)

• ICH Guideline for Good Clinical Practice E6 (R1) - Section 5.5.3
Available FDA Guidance for Industry on EDC


- Guidance for Industry: Electronic Source Data in Clinical Investigations (September 2013)

The latter three guidance documents are to be used together.
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- 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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Discussion

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