ePRO Science and Innovation: BYOD Approaches and Equivalence Across Administration Modalities

SIXTH ANNUAL

PATIENT-REPORTED OUTCOME CONSORTIUM WORKSHOP

April 29 - 30, 2015 ■ Silver Spring, MD

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Session Participants

Moderator

- Sue Vallow, Head, Patient Focused Outcomes, GlaxoSmithKline

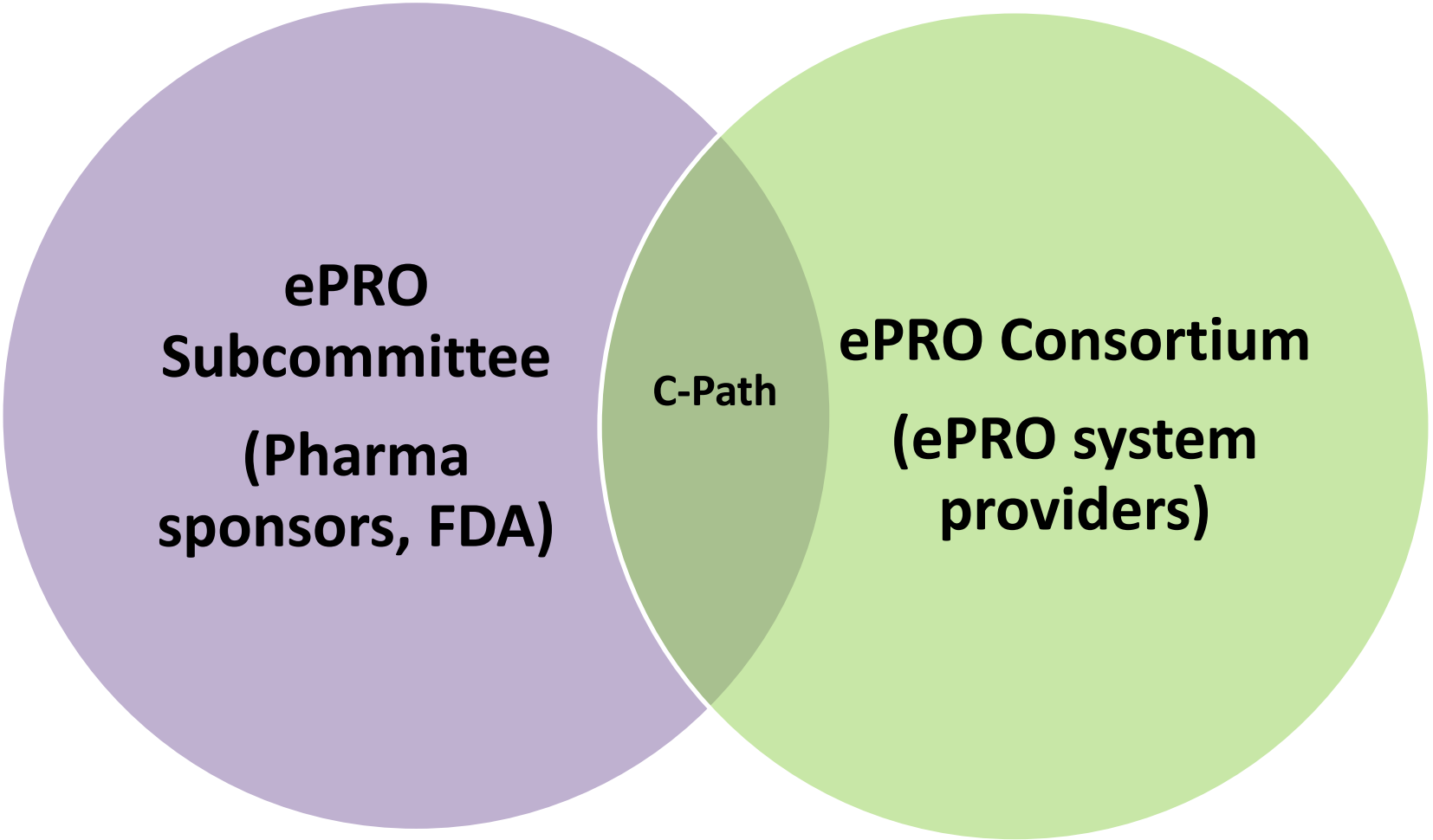
Presenters and Panelists

- Wilhelm Muehlhausen, Vice President, Head of Innovation, ICON
- Chad Gwaltney, Chief Scientist and Regulatory Advisor, Endpoints, ERT
- Virginia E. Kwitkowski, Associate Director for Labeling, Division of Hematology Products, Office of Hematology Oncology Products, FDA
- Cindy Howry, Vice President, Product Strategy and Innovation, YPrime and Vice Director, ePRO Consortium
- Sheila Rocchio, Vice President, Marketing & Strategy, PHT

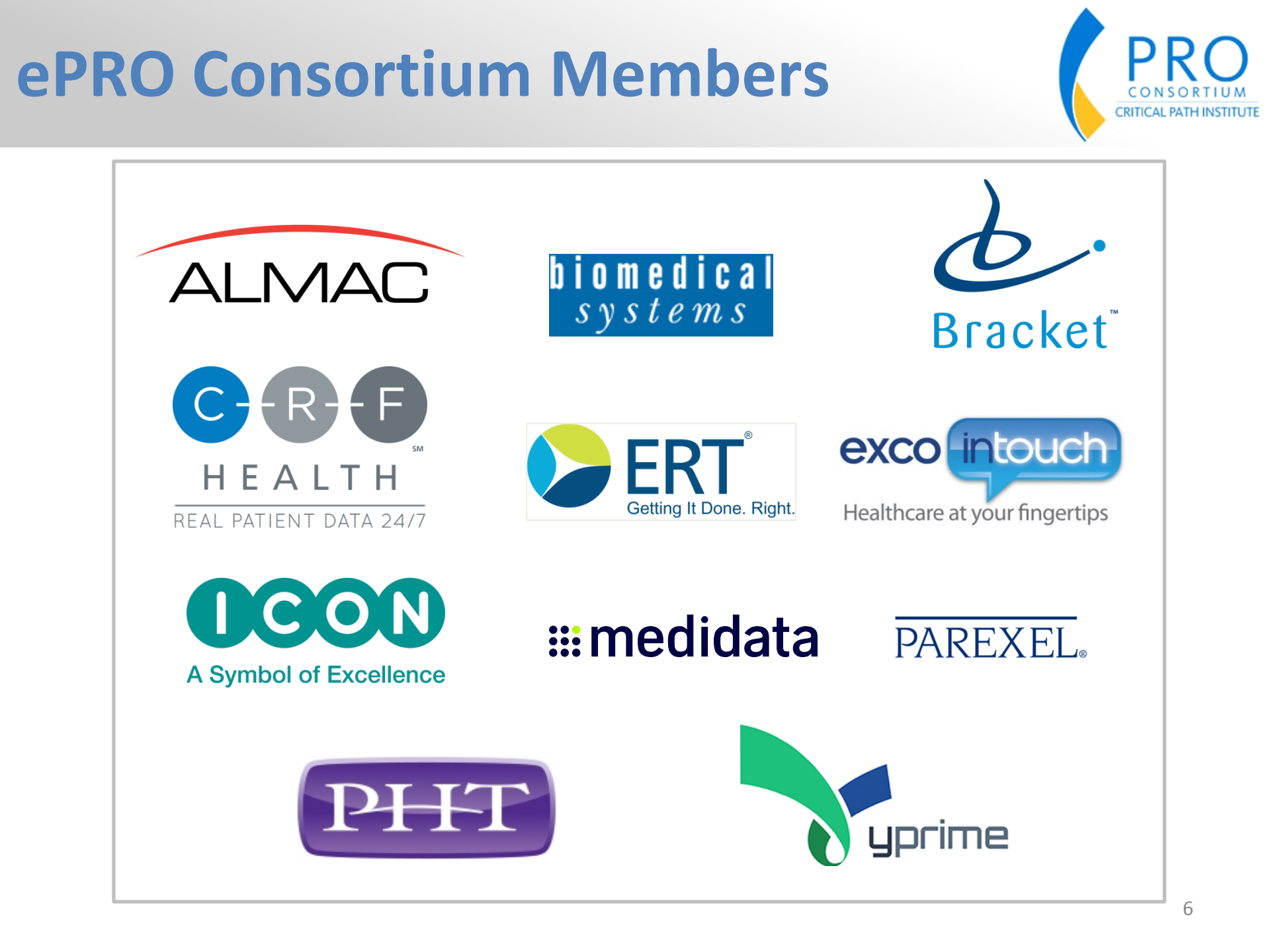
Session Outline/Objectives

- Summarize recent studies examining the equivalence of paper and electronic instruments and discuss implications for industry
- Describe recent technological and scientific advances in ePRO
- Outline current operational and scientific status of BYOD approaches to data collection

ePRO Consortium vs. ePRO Subcommittee of the PRO Consortium



ePRO Consortium Members



Equivalence of Electronic and Paper Administration of Patient-Reported Outcome Measures: A Systematic Review and Meta-Analysis of studies conducted between 2007 and 2013

Wilhelm Muehlhausen
Vice President, Head of Innovation, ICON

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Session Outline/Objectives

- Research Project description
- Review of findings and discussion
- New scientific project
- What does this mean for BYOD
- Next steps

Research project - Hypothesis

- Measurement Equivalence between original paper and migrated electronic versions does not need to be tested via quantitative (Equivalence Study) nor qualitative (Cognitive Debriefing) study, if the migration follows best practice guidelines as published by ePRO consortium and others.

Research project

- Systematic literature research 2007-2013
- Included IVRS
- Analysis of
  - Overall Equivalence
  - Device Type
  - Date of Project/Publication
  - Duration of Interval between Administrations
  - Study Design
  - Mean Age of pts
  - Publication bias

Research project

- 72 studies out of 1997 records
- 23 different population types (mental health)
- Age range from 9 – 68 years
- 435 individual correlations
- Web/PC, Handheld, Tablet, IVRS

Research project

- Pooled correlation coefficient (ICC): 0.88
- Agreement was higher in more recent studies, randomized studies and shorter intervals (<1day)
- ICC for Paper instruments to IVRS: 0.82
- Publication Bias – needs 123 additional projects with ICC of 0.65 to bring overall to <0.75

So what?!

- Don´t need equivalence studies (IVRS?)

- Need standard for equivalence studies
- Need publication standard (incl. Screenshots)

- Need further research…….

Equivalence and Device Size

- Equivalence studies tend to assume that patients are using a PC or large tablet/pad
- Use of smaller devices to access the web is increasing.
  - How do we know?
  - How much does it matter?
- Need for studies that explicitly look at design and validity over a range of device sizes

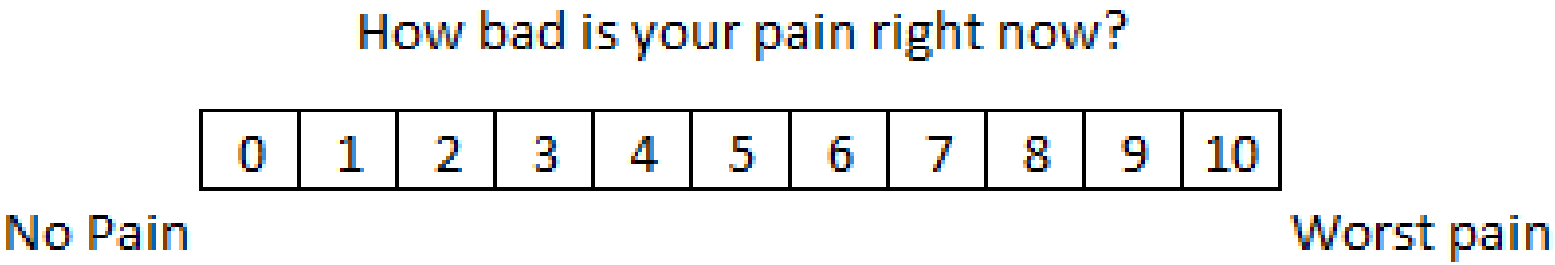
Source: Brian Tiplady, 2011

New Research projects

- Meta-Analysis by population
- Meta-Analysis by widget / scale
  - Contacted all authors
  - Reviewing submitted screens / paper versions

“Instrument Widgets”

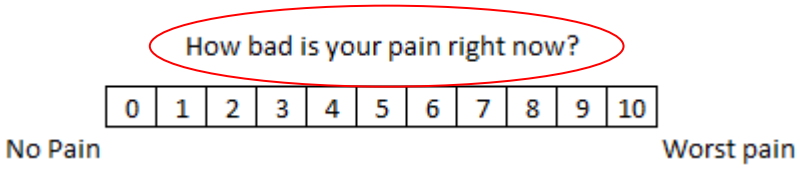
- Definition:
- A **graphical control element** or **widget** is an element of interaction in a graphical user interface (GUI), such as a button or a scroll bar.
  - „Control“ or „Widget“ is an interface element (i.e. NRS)



Instrument “Controls” / “Widget”

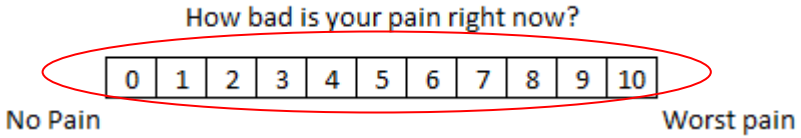
- Definition:
  - NRS has standard elements:

    1. Question



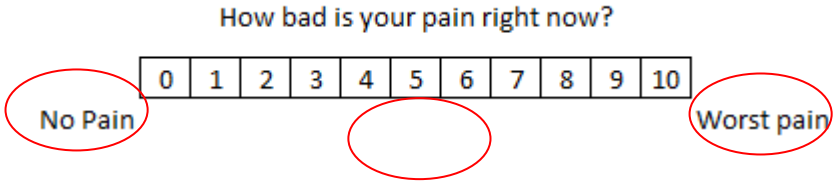
Instrument "Controls"

- Definition:
  - NRS has standard elements:
    1. Question
    2. Response Option

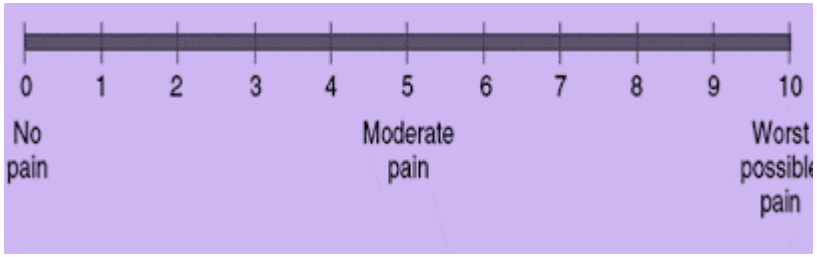


Instrument "Controls"

- Definition:
  - NRS has standard elements:
    1. Question
    2. Response Option
    3. Textual Anchors



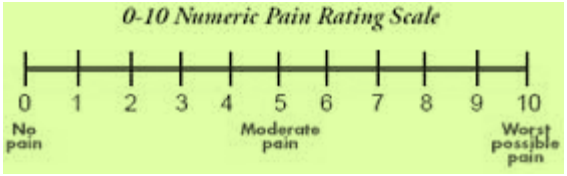
“Instrument Widgets”



How bad is your pain right now?

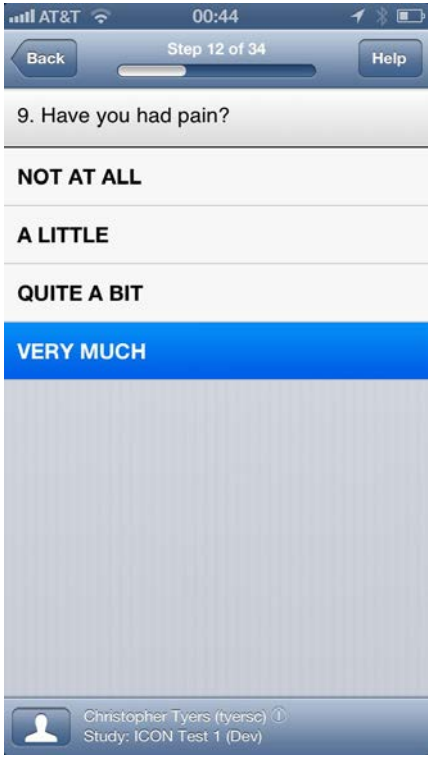
0	1	2	3	4	5	6	7	8	9	10

No Pain Worst pain



Are these the same?

	Not at All	A Little	Quite a Bit	Very Much
Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
Have you had pain?	1	2	3	4



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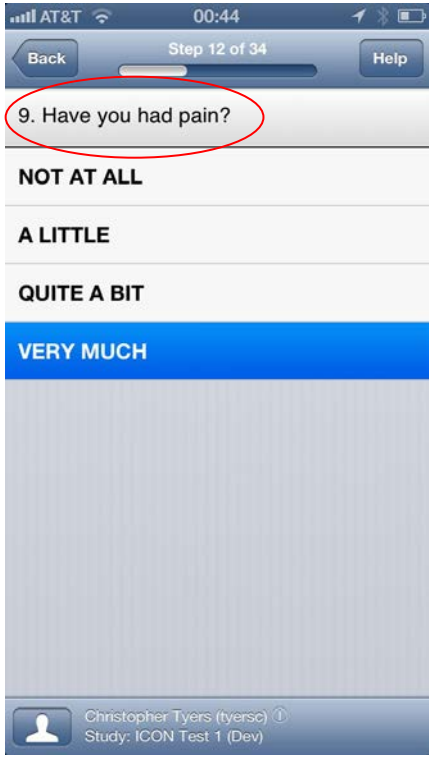
Question



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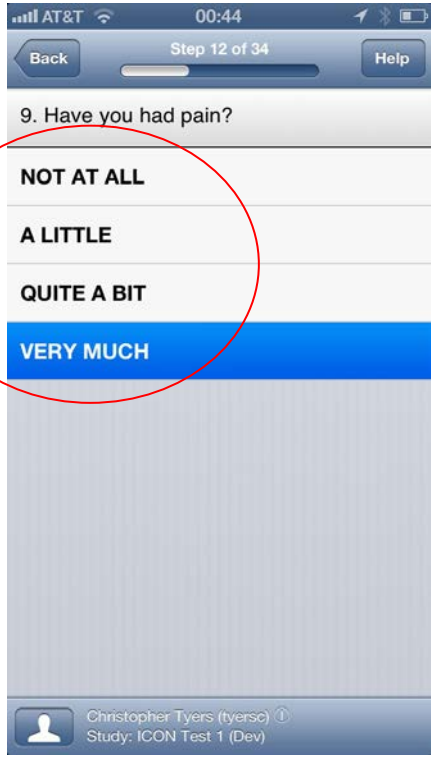


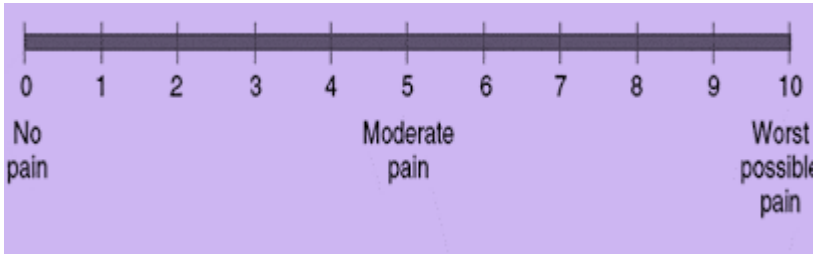
Question

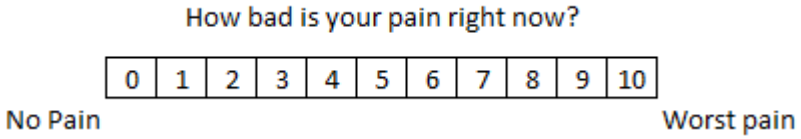
Answer Options

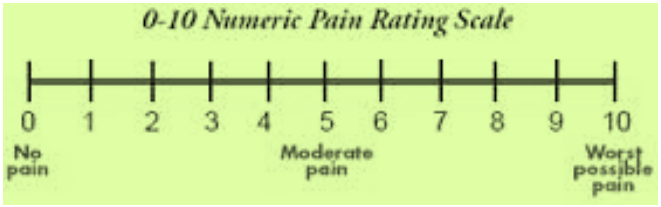
So what can you do?

- Need publication standard (incl. **Screenshots**)
- Need **HELP** for further research: screenshots of
  - Unpublished Equivalence Studies
  - Unpublished Cognitive Debriefing / Usability Tests
- Need “Widget” standard for paper AND eVersions

“Instrument Widgets”







Contact

Thank you - Danke Schön

Willie Muehlhausen

Willie.Muehlhausen@ICONplc.com

"Bring Your Own Device" (BYOD) Approaches to the Collection of PRO Data in Clinical Trials

Chad Gwaltney, Ph.D.
ERT

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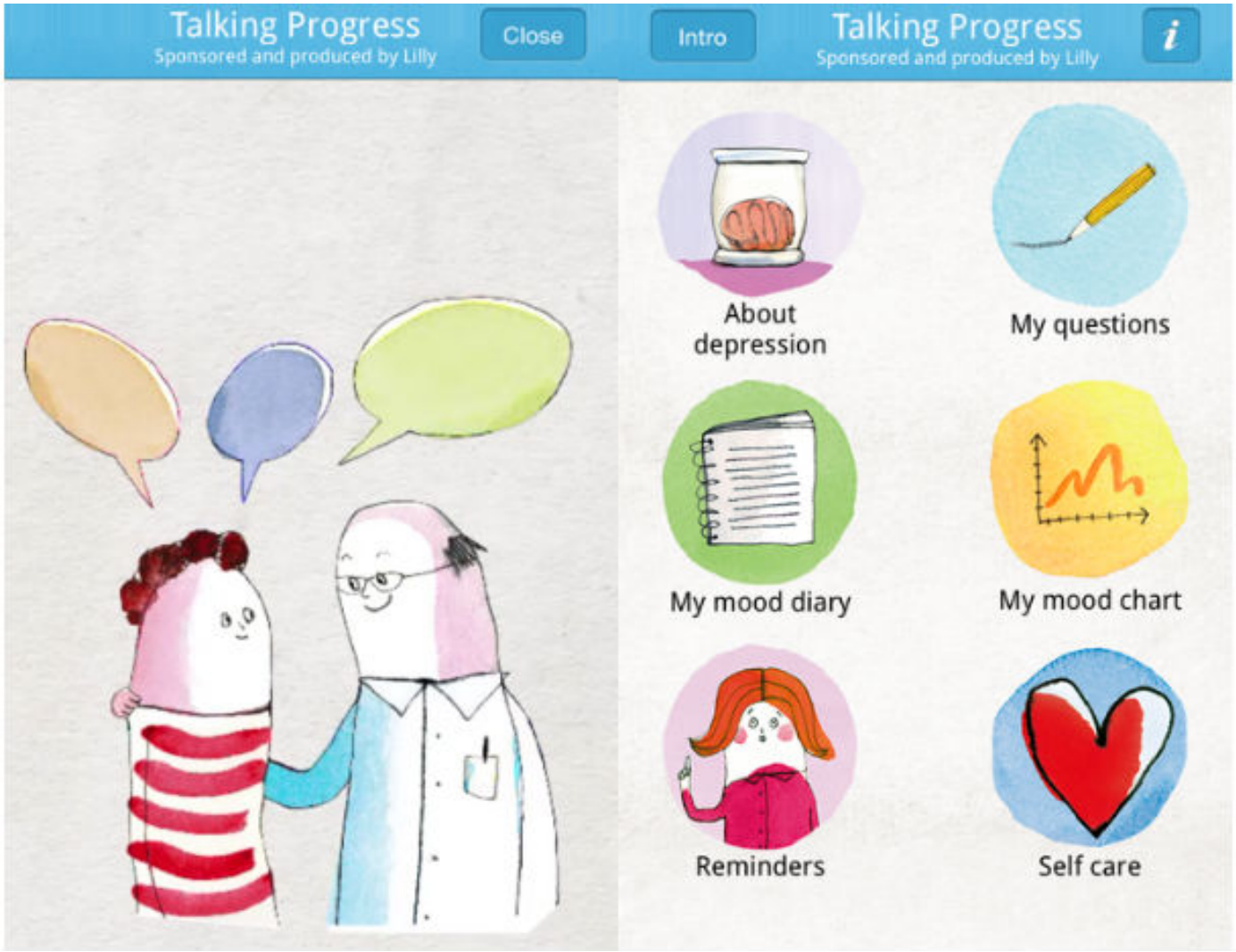
Session Outline/Objectives

- Define BYOD
- Review scientific and operational advantages
- Discuss scientific and operational challenges and open questions
- Next steps

Consumer Health and Wellness Trends

Patient Self-Report on Consumer Apps



Patient Devices As Research Tools

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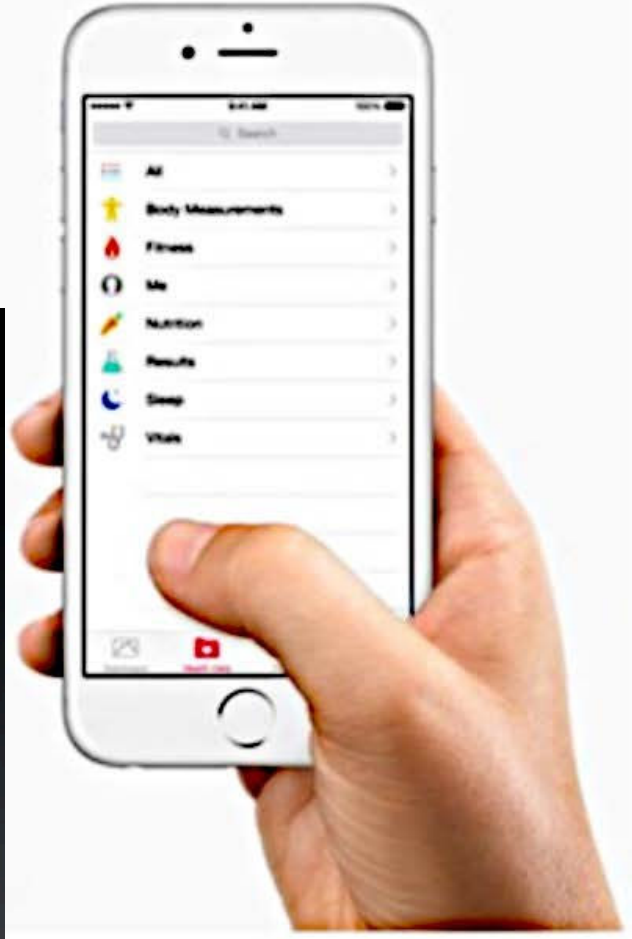
You're already carrying a powerful medical research tool.



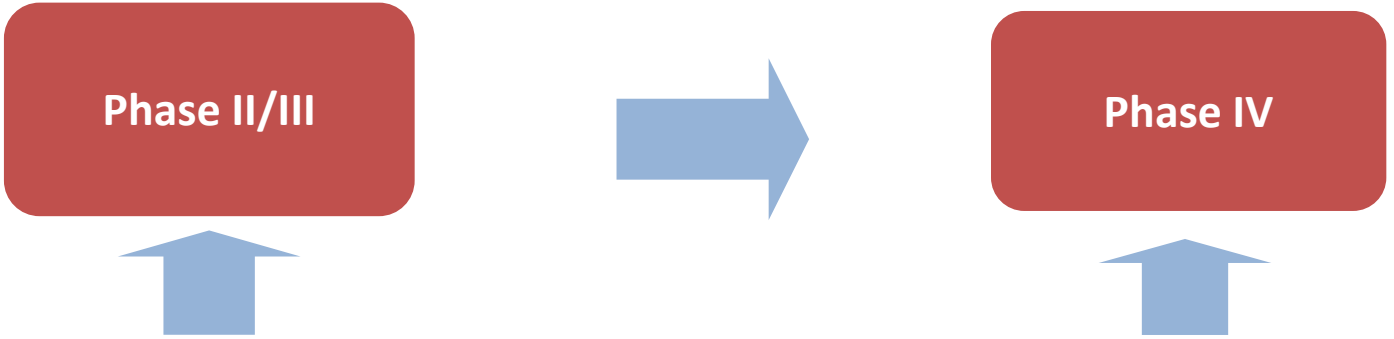
What Defines A BYOD Approach?

- Patients' use their own computers/telecommunications devices to gather ePRO data in a research study
- ePRO assessments are delivered through Web-based or app-based program
- Patients can access the assessments on different types of platforms
  - Different categories of devices (e.g., smartphones, tablets) and different models within a single category (e.g., Apple, Android)

Why Use BYOD?

Feature	Value
No devices to buy/lease, No logistics to manage	**Lower cost** **Decreased time**
Patients can use devices that they already own and use throughout the day	**Familiarity with device, always-on → High compliance (?)** **Little or no training required**
Implemented on commercial devices that are widely used across global regions	**Potential worldwide reach** **Ideal for very large trials**
Web or App-based option	**Maps onto trend towards using apps/devices to self-monitor health and behavior**

BYOD Contexts



Considerations

- Smaller-scale, internal validity key
- PRO endpoint(s) used to support approval/labeling
- Regulatory context unclear
- Additional scientific evidence needed(?)

Considerations

- Larger scale, external validity key
- PRO endpoint(s) used to understand real-world effects
- Multiple stakeholders who value real-world data
- Ready to implement(?)

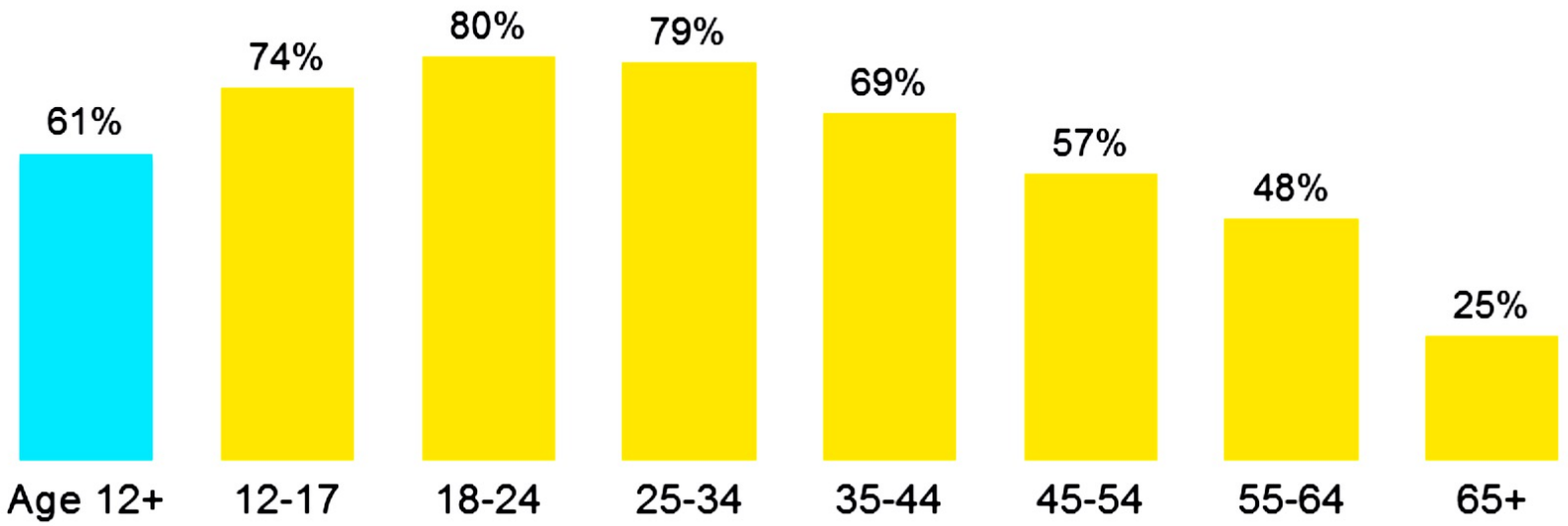
Open Scientific Questions

- BYOD is driven by ePRO science
- Smartphone and internet penetration is substantial but incomplete
  - Samples may be biased in ways that could impact trial results (e.g., age, global region, SES)
  - Provisioning of devices required?

US Smartphone Ownership

Smartphone Penetration by Age Demo

% by Age Group Who Own a Smartphone



edison research

TRITON

Open Scientific Questions

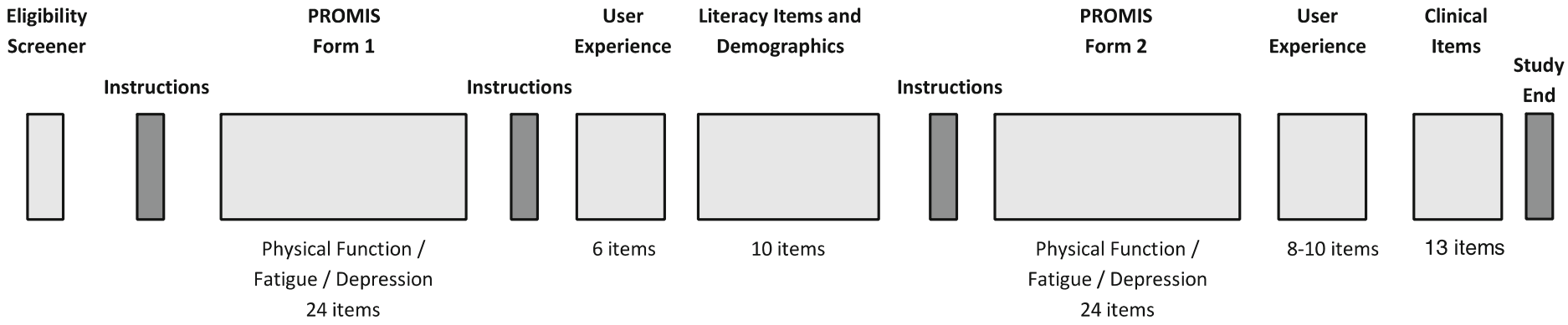
- BYOD is driven by ePRO science
- Smartphone and internet penetration is substantial but incomplete
  - Samples may be biased in ways that could impact trial results (e.g., age, global region, SES)
  - Provisioning of devices required?
- Impact of using own device on compliance
- Mixed modalities may introduce error and bias
  - Variation across and within patients

Examining Mixed Modes of Administration: A Case Study

- Bjorner, J.B., Rose, M., Gandek, B., Stone, A.A., Junghaenel, D.U., & Ware, J.E. **Difference in Method of Administration did not significantly impact item response: An IRT-based analysis from the Patient-Reported Outcomes Measurement Information System (PROMIS) Initiative**, Quality of Life Research, 2013, DOI:10.1007/s11136-013-0451-4.
- Bjorner, J.B., Rose, M., Gandek, B., Stone, A.A., Junghaenel, D.U., & Ware, J.E. **Method of administration of PROMIS scales did not significantly impact score level, reliability, or validity.** Journal of Clinical Epidemiology, 2014, 67, 108-113.

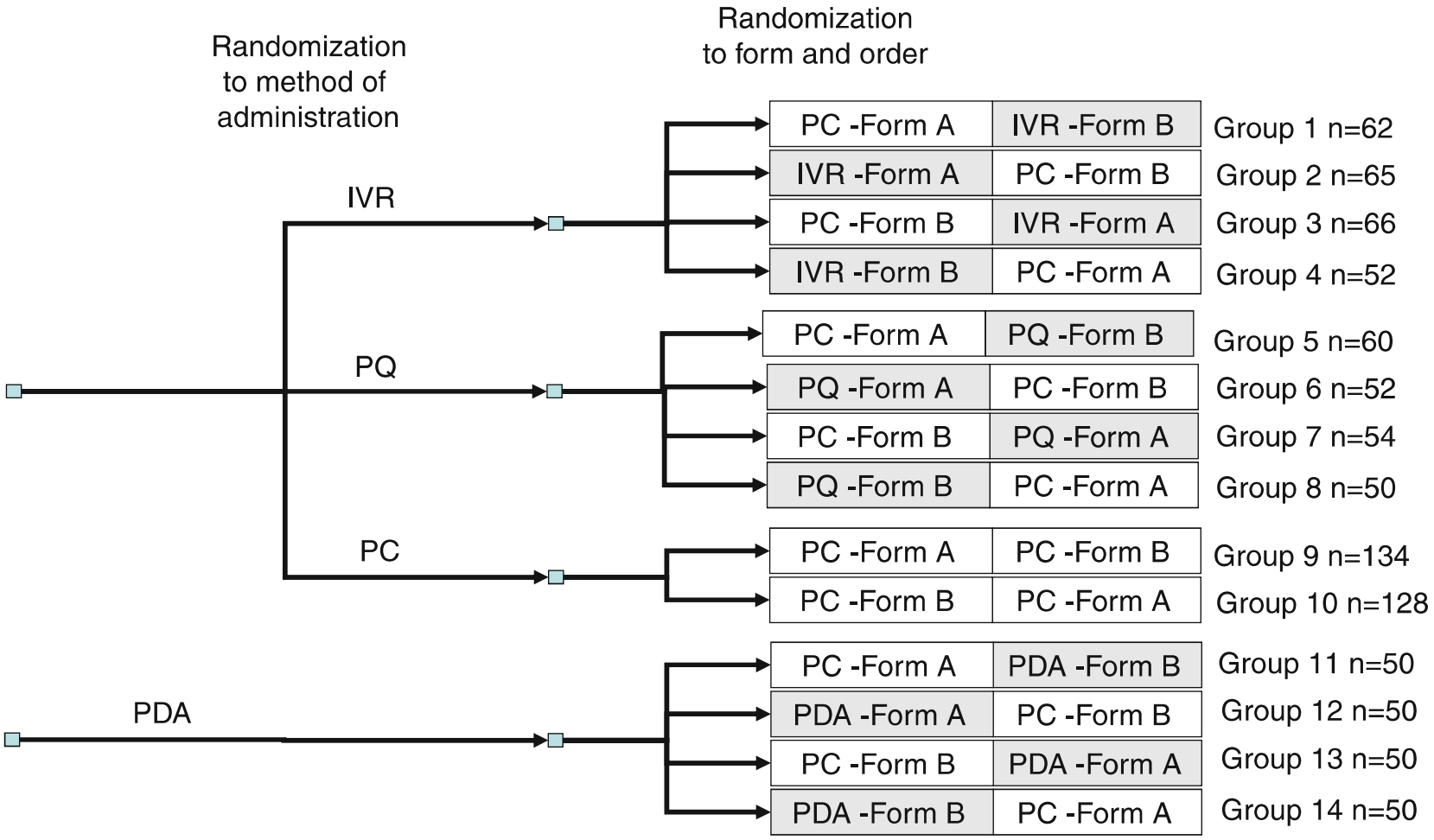
Mode of Administration

- Each participant received two MOAs, separated by other questions



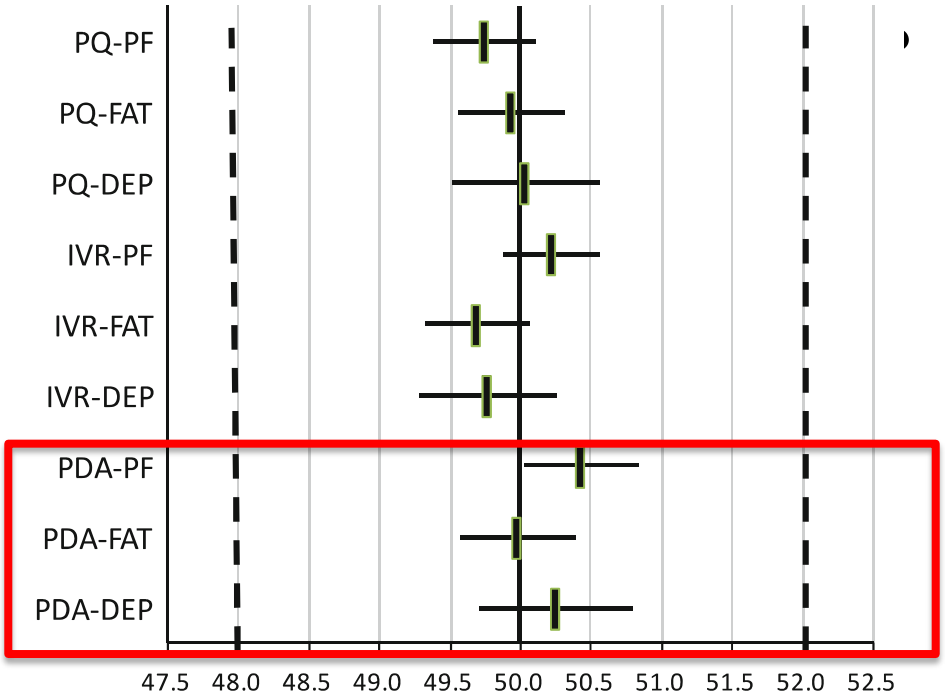
Bjorner et al., 2013

Mode of Administration



Bjorner et al., 2013

Mode of Administration



- Results
  - Few differences were significant
  - Effects were very small, well below the MID

Bjorner et al., 2013

Answering Questions with Evidence

- Need a study or studies with use of BYOD in clinical trial setting
- Compare BYOD to dedicated devices
  - Is compliance different?
  - Is there any difference in scores derived from each modality?
  - Relationships with other criterion variables (convergent validity)
- Systematically compare scores from different screen sizes

Examples of Operational Considerations

- What is the ability of the software vendor to completely remove the app, participant data, and metadata at the completion of trial participation?
- If there is a change to the device (upgrade operating system, upgrade device, lost device) during the trial, how does that affect the BYOD solution?
- Does the BYOD app add to battery drain for participants' devices?
- Payment for data plans?
- Security of app and data on personal devices?
- Can have operational discussion during Q&A

Conclusions

- Consumer trend towards using personal devices to monitor health and wellness
- Technology already exists for use in clinical trials and is commercially available
- To a degree, technology has outpaced science
- Need evidence to support the use of BYOD, particularly in pre-approval area
- How do we move forward?
  - Industry/Consortia/Regulator/Vendor collaborations

Regulatory Perspective on "Bring Your Own Device" (BYOD)

Sixth Annual Patient-Reported Outcome Consortium Workshop
April 29-30, 2015 Silver Spring, MD

Virginia E. Kwitkowski, MS, ACNP-BC

Clinical Team Leader and Associate Director for Labeling,
Division of Hematology Products
Office of Hematology Oncology Products/OND/CDER

Disclaimer

This presentation reflects the views of the author and should not be construed to represent FDA's views or policies.

Available FDA Guidance

- None specific to BYOD
- Guidance on ePRO available in:
  - Regulations: 21CFR Part 11 "Electronic Records"

    http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=11&showFR=1&subpartNode=21:1.0.1.1.1.8.2
  - Guidance: Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims

Why Is ePRO Better Than Paper?

Device-Specific Regulatory Issues

- Comparability of data obtained via different collection methods
- Device should be available to entire enrolled population
- Assure that replacement devices available in case of device failure or lost device
- Date and time stamp ePRO entries

Data Related Regulatory Issues

- Sponsors must…
  - Ensure that FDA regulatory requirements are met for record keeping, maintenance, and access
  - These responsibilities are independent of method used to record data
  - Control, access and maintain source documentation

Who Controls the Data?

- Direct control over source data should be maintained by Investigator so that verification of source data can occur at the time of FDA inspection.
- 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.

What to Avoid

- Direct PRO data transmission from the PRO data collection device to the sponsor, clinical investigator, or other 3rd party without an electronic audit trail that documents all changes to the data after it leaves the PRO data collection device.
- Source document control by sponsor exclusively
- Existence of only one database without backup
- Ability of any entity of than INV to modify the source data

Examples of Labeling Claims Generated by ePRO Data

Jakafi® -Incyte Corporation (2011)

- –Myelofibrosis Symptom Assessment Form (MFSAF) v2.0 handheld diary (*symptoms*)

Subsys® -insys Therapeutics, Inc. (2012)

- –Visual Analogue Scale handheld diary (*pain*)

Linzess™ -Ironwood Pharmaceuticals & Forest Laboratories (2012)

- –11-point NRS of Abdominal Pain at its Worst –IVRS (*abd pain*)

The Future is Here

- Though our office hasn't seen a completed trial using BYOD, there is evidence that there are ongoing trials in other areas at FDA:
  - Phase 2 pharmaceutical trial in patients with hypoactive sexual desire disorder (n=200)
  - Medical device trial with additive for pain relief in Europe (device is for cheek shaping); instrument measuring pain (n=50)
  - Phase IV trial in Japan to test three types of hyaluronic acid injections in patients with osteoarthritis of the knee; measures QoL (n=600)

Summary of BYOD Considerations

Ensure:

- Consistency between formats
- That all enrolled patients have devices (or one is provided to them)
- Availability of backup device should failure of primary device occur (avoid missing data)
- Data entry date/time documentation

References

- PRO Guidance- [http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM193282.pdf]

- 21CFR11: Part 11 Electronic Records [http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=11&showFR=1&subpartNode=21:1.0.1.1.8.2]

Discussion and/or Questions?

Discussion/Questions

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- Cindy Howry, Vice President, Product Strategy and Innovation, YPrime and Vice Director, ePRO Consortium
- Sheila Rocchio, Vice President, Marketing & Strategy, PHT