

Web-based ePRO: Validation, Equivalence, and Data Quality

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Web-based ePRO: Outline

- Benefits of electronic patient-reported outcomes (ePRO)
- Why use the web for ePRO?
- Aspects of the web that may affect our data
- Validation: Are we measuring what we think we are measuring?
- Equivalence: Does the web give the same results as other modalities?
- Data Quality: Compliance, completeness, consistency, and bias

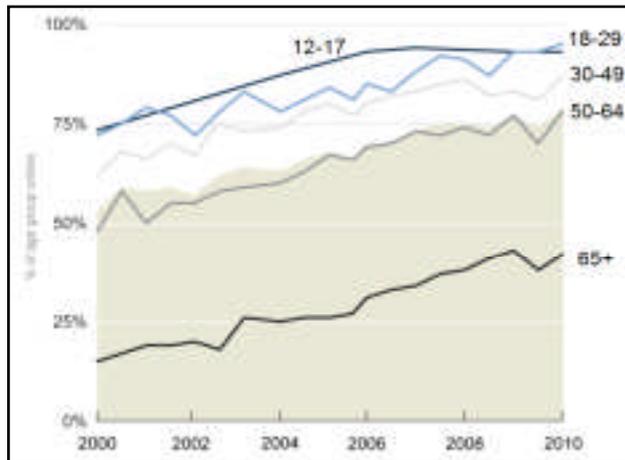
Benefits of ePRO

- Only valid, in-range data can be entered
- Missing data can be reduced or prevented
- Feedback to help patient compliance
- Automatic question-branching
- Time-stamping of entries
- Manual data editing and entry eliminated
- Rapid review of data on web server
- Well-established, reliable technology
- Highly acceptable to patients

Why the web? - Access

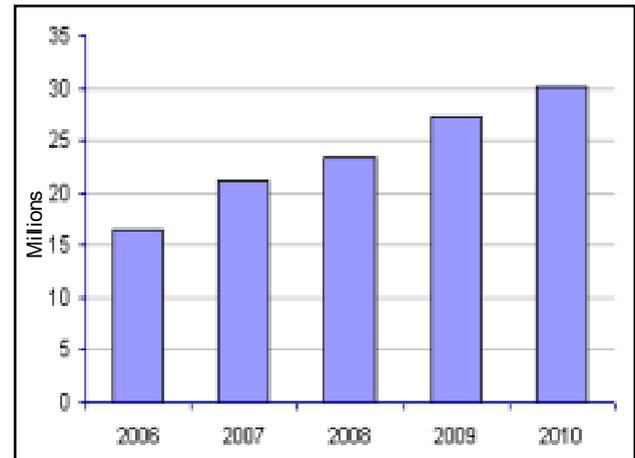
USA

Internet usage by age



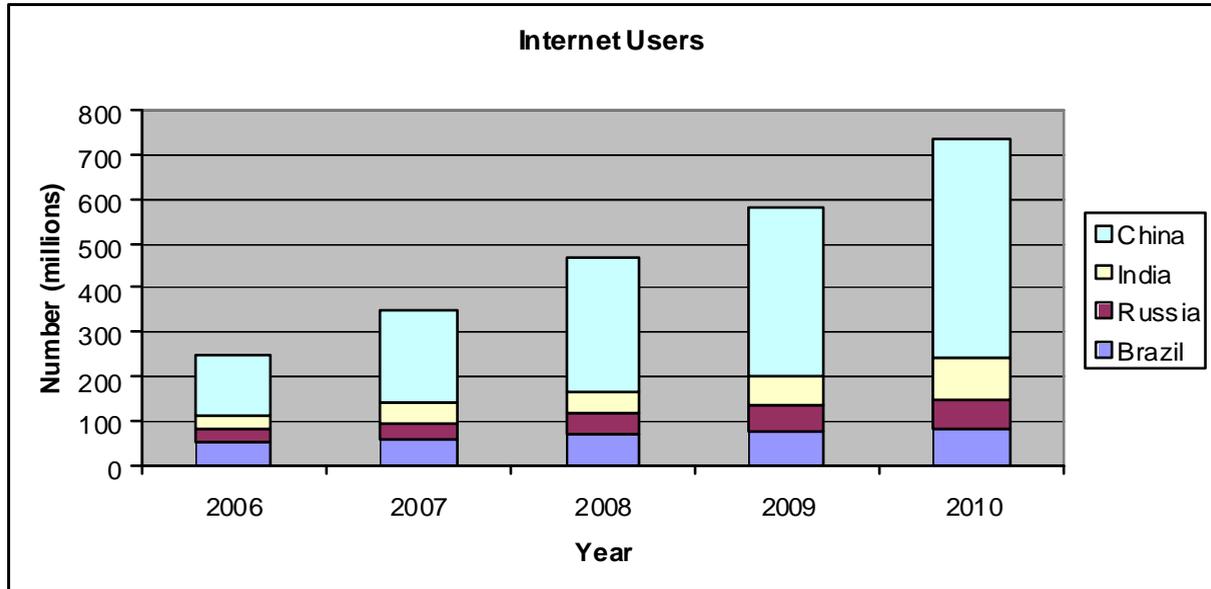
UK

Adults using the internet everyday



(Source: UK Office of National Statistics)

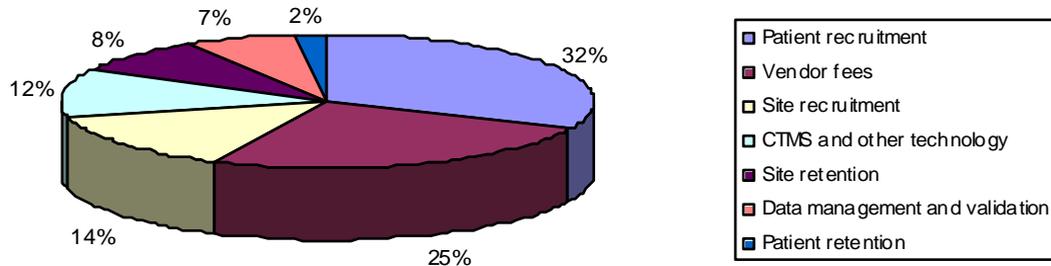
Why the web? - Access



Source: World Bank, World Development Indicators, 2011

Why the web? - Recruitment

- Clinical trial costs*:



- Availability of large patient samples
 - Content validity of outcome measures
 - Surveys of course of illness and adverse events

* *Clinical Operations: Benchmarking Per-Patient Trial Costs, Staffing and Adaptive Design*, Cutting Edge Information, 2011

Why the web? - Technology

- Use of existing equipment for web data collection
- Integration with EDC systems
- Mobile web applications
- Improved user interfaces
 - Touchscreens
 - Graphical/iconic presentation

Web Options in Clinical Research

Model	Recruitment	Equipment
<p>Closed (conservative)</p>	<p>Through clinic/study site, identifiable patients with medical records</p>	<p>Supplied by sponsor</p>
	<p>Through web, patient identity known</p>	<p>Vetted by sponsor, e.g. screen size, type of input</p>
<p>Open (innovative)</p>	<p>Through web, anonymous patients</p>	<p>Whatever the patient uses</p>

Validity

- Relevant and comprehensive content
- Correlation with external criteria
 - Other scales
 - Clinician interview
 - Key events
 - Physiological measures
 - Discrimination between known groups
- Internal consistency
- Stable factor structure

Web-based Data Collection: A Validation Example

- Little web-based ePRO work from clinical trials has been published
- Data available in three main areas
 - Clinical care programmes
 - Patient support groups in specific conditions
 - Adverse event monitoring
- Experience from these areas is highly relevant to clinical trials

Recovery after Prostate Surgery

- Patients often suffer from urinary incontinence and erectile dysfunction
- Function generally improves, but uncertainty over this causes much anxiety
- Physicians tend to underestimate extent of problems compared to patient reports
- Web-based ePRO solution developed to record the patient's perspective on functional recovery
- Data made available to physicians at clinic visit

The Web-based ePRO Instrument

- Questions on:
 - Erectile/Sexual function
 - Urinary function
 - Bowel function
 - General Health
- Interactive features
 - Skip logic
 - Questions on time at which function improved
- Patients (N=1235, aged 57-67) completed web questionnaire at home following reminder emails

Validation Outcomes

- Expected associations between urinary and sexual function and
 - Age
 - Time from surgery
 - Nerve-sparing status
 - Co-morbidities
- Cronbach's alpha 0.84 – 0.97
- Much higher correlations with domains (0.54 – 0.83) then between domains (0.15 – 0.31)

Source: Vickers et al. (2010)

Prostate Study: Conclusions

- Criterion validity
 - all expected associations were found
- Discriminant validity
 - Lower correlations between than within domains
- Internal Consistency
 - High values for Cronbach's alpha
- No data presented, or needed, for paper-electronic equivalence
- Methodology appropriate for supporting clinical trial use of web-based ePRO

Web-based Content Validation

- Content analysis of PatientsLikeMe.com online community used to develop survey of treatment adherence (MS-TAQ)
- Cognitive interviewing of small face-to-face sample
- Sample recruited from PatientsLikeMe completed survey online
 - 431 complete from 1209 invited
 - Patients had similar sex ratio to those in previous face-to-face sample, but were slightly younger (47 vs 51), and had disease for slightly shorter time (11 vs 9 yrs)
 - Significant correlations between compliance and “Barriers” (0.50) and “Coping” (-0.30) subscales, supporting scale validity

Source: Wicks et al. (2011)

Equivalence Studies

When do we need equivalence studies?

- When a PRO instrument has been validated in paper form, and we wish to use that validation data to support electronic use
- When we wish to use paper and electronic data interchangeably
- If an instrument is developed from the start in electronic form, no comparison with paper is needed

Paper is not the gold standard!

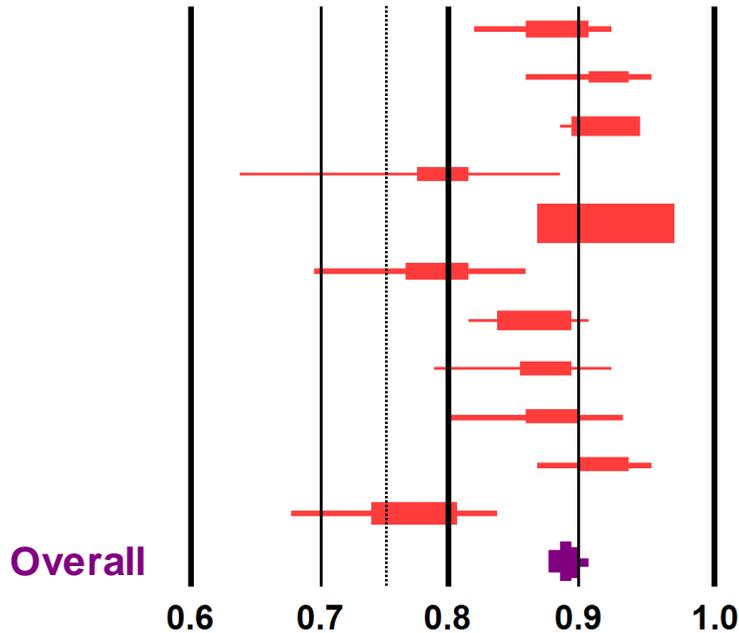
But establishing equivalence is often useful

Establishing Equivalence

- Meta-analysis conducted on 14 published studies with adults completing web-based and paper PRO instruments in a crossover design
- Good agreement between web and paper
 - Average weighted correlation 0.884 [CI: 0.870-0.897]
 - No significant difference between home and lab/clinic completion
 - Mean overall difference between web and paper 0.2% of scale range
 - Mean absolute difference 1.7% of scale range

Source: Tiplady and Gwaltney, publication in preparation

Web-paper Correlation



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 - How much does it matter?



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- 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



Data Quality and the Web

- Many aspects of data quality are similar to those with electronic methods in general:
 - Avoidance of accidental missing data
 - Prevention of invalid or non-codable responses
 - Time-stamping of responses
 - Ensuring applications are straightforward to use in an unsupervised setting
- Possibility of bias

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 - Women now use the internet as much as men
 - Older people are increasingly using the internet
 - Mobile devices are making the internet more and more accessible



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 - Mobile devices are making the internet more and more accessible
- The internet can reach people in new ways that may help overcome old forms of bias.



Drug Safety

- Under-reporting of adverse drug reactions is a long-standing problem in safety surveillance
- Physicians consistently under-estimate severity of symptoms (both of disease and of drug reactions) compared to patients

Lopez-Gonzalez et al. (2009)
Basch et al. (2009)

PROs in Drug Safety

- PRO-CTCAE programme
 - ePRO system, not specifically web-based
 - Web-based system based on CTCAE items developed and tested in cancer outpatients
- Online patient communities may provide broadly-based samples for investigating drug safety

Web-based Safety Monitoring

- iGuard.org (MediGuard) is an established site set up by Quintiles to monitor patient medication, with more than 2.5 million patients enrolled
- Patients take part in surveys of a wide variety of treatments
- Survey is similar to PRO instruments
- Not compliant with regulatory requirements
 - Patients not identifiable
 - Part 11 etc.
 - Exploratory studies generating hypotheses to be confirmed in other ways

Web-based Safety Monitoring

- Atypical antipsychotic survey (Cascade et al., 2010)
- 54% experienced a side effect
 - Weight gain/Hunger
 - Tired
 - Muscle twitch, tenderness, tremor
 - Lack of coordination
- Most adverse events were not reported to patient's doctor

Web-based ePRO: Conclusions

- The web is increasingly important for data collection in clinical research
- Web data collection can give valid data in unsupervised environments
- Web tools are useful in developing PROs and ensuring content validity
- Web and paper versions of the same instruments give closely similar results
- Care must be taken to deal with potential sources of recruitment bias in web-based studies
- The broad reach of the web may help to overcome some sources of bias in clinical data collection

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