

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

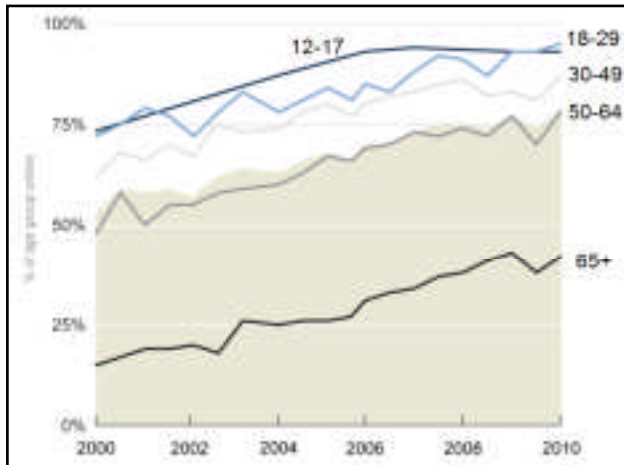
Benefits of ePRO

- 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

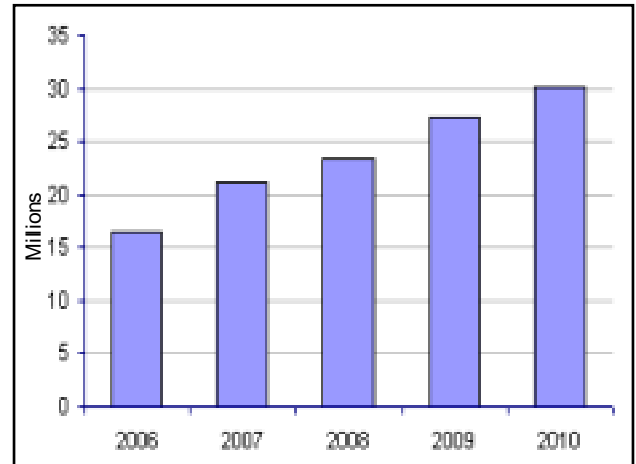
USA

Internet usage by age



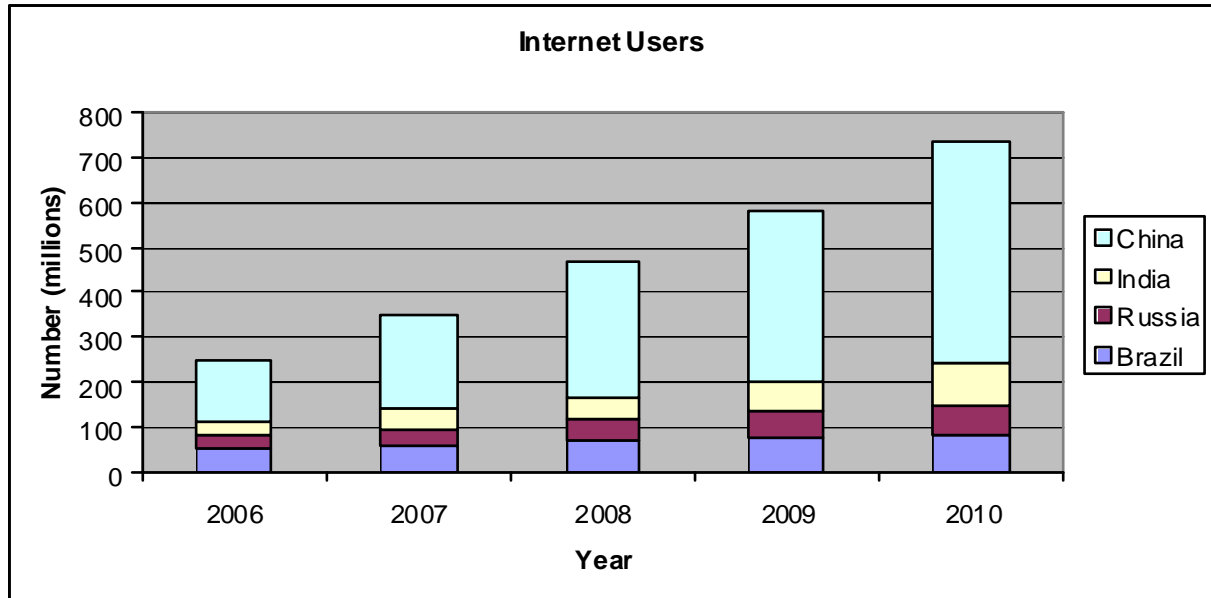
UK

Adults using the internet everyday



(Source: UK Office of National Statistics)

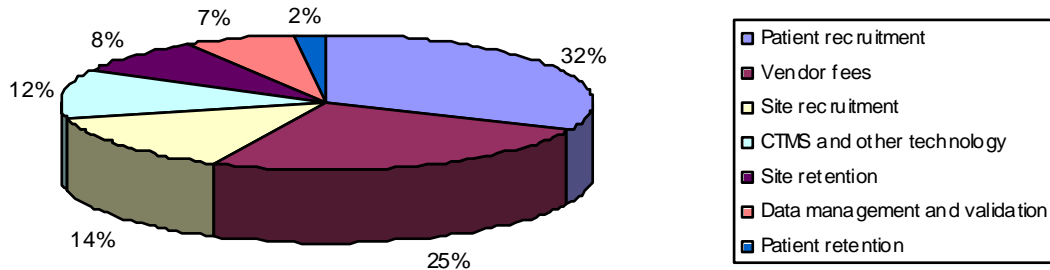
Why the web? - Access



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

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!

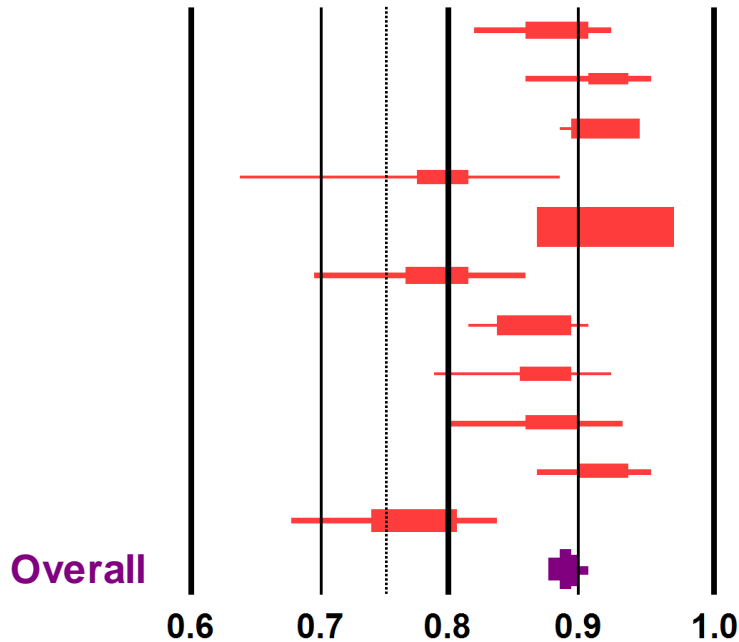
But establishing equivalence is often useful

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



Equivalence and Device Size

- Equivalence studies tend to assume that patients are using a PC or large tablet/pad

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 - How do we know?
 - How much does it matter?



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



Data Quality and the Web

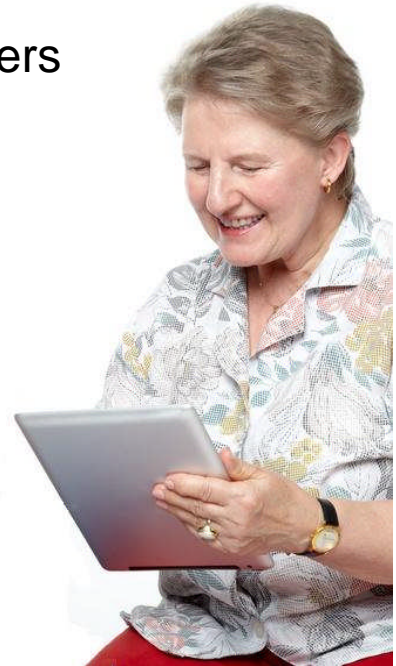
- Many aspects of data quality are similar to those with electronic methods in general:
 - Avoidance of accidental missing data
 - Prevention of invalid or non-codable responses
 - Time-stamping of responses
 - Ensuring applications are straightforward to use in an unsupervised setting
- Possibility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

Bias and the Web

- Those using the internet differ from non-users
 - Younger
 - Higher educational status
 - More affluent

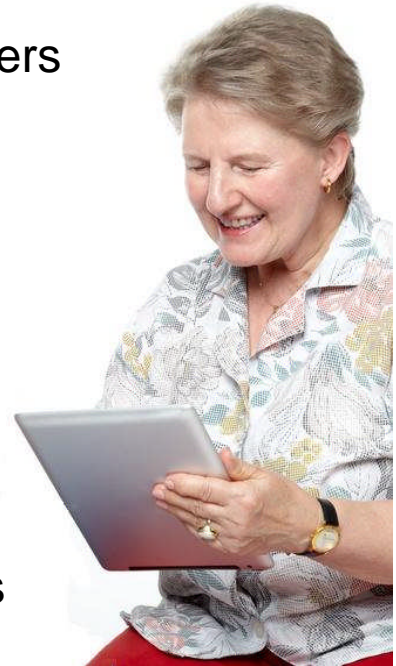
Bias and the Web

- Those using the internet differ from non-users
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- The digital divide is diminishing
 - 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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 - Women now use the internet as much as men
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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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