Good Questions

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Why use electronic patient-reported outcomes (ePROs)?

by Keith Wenzel

Use of electronic patient reported outcomes (ePRO) is increasingly considered essential for clinical trials. The rapid adoption of ePRO is the result of three core areas of advantages: data integrity, regulatory support and organizational mandate.

Data Integrity

Early adopters of ePRO were drawn by the data integrity advantages; computers have the ability to consistently administer an instrument in a standardized and objective manner. In addition, for instruments with scoring or skip patterns (also known as branching), clinical trial Sponsors have historically spent tens, if not hundreds of thousands of pounds, euros, dollars, etc. for each trial checking and/or cleaning paper-based PROs. With ePRO, the instrument author and the Sponsor can be confident the instrument is administered in a consistent fashion with the appropriate branching, if applicable, of original instrument design.

The limitations of paper-based PROs, especially when it comes to the "parking lot effect", where study participants retrospectively (and sometimes even prospectively) enter data, are well recognized. Electronic PROs date and time stamp data, so the Sponsor and the regulatory agencies have complete transparency as to when the data were collected. As a result, all parties have greater insight into how a study participant's treatment (or placebo) is affecting the disorder being studied. Interestingly, because we know exactly when the data were collected, Sponsors are learning more about the waxing and waning conditions of their patients; this helps Sponsors create profiles or groupings of patients for disorders to better understand the therapeutic effect of their compounds in different manifestations of the disorders being studied.

Regulatory Support

The EMEA's 2005 Reflection Paper on Health-related Quality of life and the FDA's 2006 draft guidance on patient reported outcomes brought renewed industry focus to PROs and, by extension, ePRO. Statements from the FDA's draft guidance like, "*…the FDA plans to review the protocol to determine what measures are taken to ensure that patients make entries according to the study design and not, for example, just before a clinic visit.*" spur adoption of ePRO because it is difficult, if not impossible, to achieve this level of documentation with paper PROs.

The EMEA also has referenced the advantages of ePRO with the following statements, *"If home recording equipment is used, reproducibility is particularly important and an electronic diary should be considered to validate the timing of the measurements.'* (CPMP/EWP/519/98) and *"A separate calculation of the Pearl Index for method failure requires reliable methods for recording of compliance (e.g. electronic patient diaries)…"* (CPMP/EWP/519/98).

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About the author

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He is a known authority on ePRO and often speaks and writes on the subject at industry conferences and in industry journals.

Health Awareness - for your diary

Pregnancy Health Month
Leukaemia & Lymphoma Awareness Month
Fibromyalgia Awareness Week (6-13)
National Eczema Week (13-19)
International Ataxia Awareness Day (25)
World Heart Day (28)

New GP contract narrows care gap between wealthy and poor

In 2004, the NHS widened their Quality and Outcomes Framework (QOF) incentive scheme to encourage GPs to take a more significant role in managing patients with long-term conditions.

Researchers from the University of Manchester have investigated the performance of more than 7,000 GP practices in England, showing that the discrepancy of standards of care between wealthy and poor areas narrowed in the first three years of the scheme. Under the new scheme, a third of doctors' income is related to their performance in key indicators such as waiting times and disease management. According to the researchers, this aspect of the deal that has played a pivotal role in improving care.

The researchers explored 48 indicators of standards of care in practices classified according to five levels of deprivation. Standards of care in the most deprived areas have improved at a faster rate than elsewhere. In the first year of the scheme, targets were met 82.8% of the time in the most deprived areas compared with 86.8% for the most affluent areas. In the third year, the care gap narrowed from 4% to less than 1%, with the poorest areas achieving 90.8% on average and the richest achieving 91.2%.

These findings were welcomed in light of the criticisms of the pay increases GPs have received under the new scheme.

In Brief

- Patients to get 'sight-saving drug'

In a complete reversal of last year's decision, the National Institute for Health and Clinical Excellence (NICE) announced recently that the sight-saving drug Lucentis is to be made available on the NHS for all people with wet age-related macular degeneration upon diagnosis (previously recommended tonly after patients lost sight in one eye). Lucentis has impressive clinical results but costs over £10,000 per eye. Some primary care trusts (PCTs) in England had already made the treatment available prior to NICE's new guidance (Aug 2008), resulting in accusations of a postcode lottery. Legal action was subsequently taken against some PCTs. This situation along with re-evaluation of the long-term cost-benefit of Lucentis contributed to NICE striking an agreement with the drug's manufacturer, Novartis: the NHS will pay for 14 injections of Lucentis (which is predicted to provide stable vision) with subsequent injections funded by Novartis.

- Clues to why some smokers get hooked at first puff

In the search for new therapies to help people quit smoking, researchers at the University of Western Ontario, Canada, have been exploring what it means to start smoking. The interaction of nicotine with certain neuro-chemical pathways within the brain usually produces either rewarding or addictive effects. However, during the first phase of tobacco exposure nicotine is often found to be an unpleasant experience associated with nausea. For some individuals, the initial phase is highly rewarding and they become dependent on nicotine very quickly. The researchers attribute this to the dopamine pathways, which are connected to nicotine's rewarding properties, also known for being involved in addictive responses to drugs such as cocaine and alcohol. If researchers can identify the dopamine sub-type receptors that control a person's initial sensitivity to nicotine, it will pave the way to reduce nicotine being processed as rewarding. This would then allow for new treatments of addiction to nicotine.

Why use ePROs?

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Some of the primary efficacy data for eszopiclone (Lunesta® in the US), for insomnia, and Climara PRO for uterine bleeding and spotting were collected via interactive voice response (IVR), a commonly used ePRO modality. In addition to paper, the FDA acknowledged in line 322 of the draft guidance that PRO collection methods include, *"…electronic, Web-based, and interactive voice response formats."*

It is important to note as with paper-based PROs, Sponsors have a responsibility to ensure appropriate record keeping. The guidance indicates, *"When electronic PRO instruments are used, sponsors should plan carefully to ensure that FDA regulatory requirements are met for sponsor and investigator record keeping, maintenance, and access."* [0]

Organizational Mandate

Many Sponsors now have organizational mandates that study teams must use electronic methods or must apply for a waiver if they with to use paper-based methodologies. Using ePRO with other electronic methodologies not only contributes to better trial execution e.g. adaptive trial designs (see below), but also results in other efficiencies. By integrating ePRO data with electronic data capture (electronic CRFs), all source data is stored in the EDC system; thus, providing a single point of access to all of the study participant's data. Another example is that an ePRO system often has the most recent data concerning the study participant's status; thus, this data, when integrated with clinical trial management system, can be used to update study enrolment/status and/or study budgets.

Adaptive trial designs often cannot be executed without the use of ePRO. In these designs, patient data are exported to a third party black box (vendor) for analysis so that the data monitoring committees may receive updates about each treatment arm's performance, or lack thereof, such that the study may be adapted appropriately.

Organizational mandates have helped broaden the breadth and depth of ePRO use. Obviously, ePRO is being used for primary and secondary efficacy data, but, remarkably, ePRO has been used successfully for a diverse range of applications including adaptive trials, comorbidity data, trial recruitment, personalised assessment of most troubling symptoms, inclusion/exclusion criteria, disorder severity assessment, screening, medication compliance and safety data collection.

Does paper have any utility?

The answer is "of course it does." Sometimes, because of the logistics (e.g. number of participants, a single site, cost/timelines pressures), paper is a more practical solution. However, for registration trials where data integrity and ensuring that study participants are providing data according to the study protocol, ePRO needs to be considered. On the right is a non-comprehensive list of some commonly cited advantages and disadvantages for paper and electronic PROs.

ePRO Validation - Good Research Practice

Any Sponsor wishing to make a PRO-based labelling claim based on electronically collected PRO data, needs to make an assessment of the amount of clinical validation required for their ePRO instrument. It is generally accepted that the FDA will likely require a PRO Dossier for PRO-based labelling claims. If a paper-based PRO instrument is migrated to electronic administration some confirmation that the instrument is still collecting the data it is intended to collect is required. The level of validation typically ranges from a cognitive debriefing to an equivalency study to a more rigorous evaluation of the ePRO instrument's measurement properties. A more detailed description of the issues involved has been submitted to *Value in Health* by ISPOR's ePRO Consensus Group. It is expected that this article will be available in electronic form by October 2008.

PAPER-based PROs

- ☑ **Established, accepted medium**
- ☑ **No/little training required**
- ☑ **Easy to produce/copy and distribute**
- ☒ **No reliable date/time stamping**
- ☒ **Vulnerable to misread / misinterpreted instructions**
- ☒ **Not able to automatically remind participants to complete**

ELECTRONIC PROs (ePRO)

- ☑ **Automated branching for skip patterns**
- ☑ **Reduced missing data**
- ☑ **Reduced data entry errors**
- ☒ **Some training required**
- ☒ **Possible additional validation burden**
- ☒ **Unfamiliar/intimidating for technophobes**

BMJ In the Journals

The benefits of open access publishing

1 Previous retrospective studies have examined the impact of open access on citations. Such research is open to self selection bias i.e. open access articles are cited more because authors choose articles to promote freely, or highly cited authors choose open access.

2 To control for self selection the authors carried out a RCT to measure the effect of free access on article downloads and citations.

3 Scientific articles published online in 11 scientific journals were randomly assigned to open access (n=247) or subscription (n=1372).

4 Downloads of full text and abstracts and number of unique visitors (ip addresses) were used as proxy measures for readership. Citations to articles were gathered after one year.

5 Full text downloads were 89% higher, PDF downloads 42% higher, and unique visitors 23% higher (all $p<0.001$) for open access articles. Abstract downloads were 24% lower ($p<0.001$) for open access articles. A logistic regression analysis estimated that open access publishing reduced the expected odds of being cited by approximately 13%.

6 These results suggest that open access increases the readership of articles but has no effect on the number of citations in the first year after publication. The citation advantage from open access reported in the literature may therefore be an artefact of other causes.

Davis PM, Lewenstein BV, Simon DH, Booth JG, Connolly MJL (2008). Open access publishing, article downloads, and citations: randomized controlled trial.

NICE comeback!

You may remember, in last month's Good Questions, we debated the wider costs of cost-effectiveness evaluation. Last week, Sir Michael Rawlins, Chairman of the National Institute for Health and Clinical Excellence (NICE) responded to recent criticisms. He suggested that an ageing society, technological advances and public expectations are placing demands that all countries are struggling to meet. In the UK, the NHS has finite resources available for healthcare and it must take account of the interests of all those who depend on the NHS for their healthcare. In direct response to recent criticism over the availability of life-saving cancer drugs, Sir Michael Rawlins explained that, since NICE was set up in 1999, it has recommended over 90 per cent of the cancer drugs it has been asked to review. These cost the NHS around £337m a year. Sir Michael Rawlins' comments are published in full in the Health Service Journal. Andrew Dillon (Chief Executive of NICE) also appeared on the BBC's recent Panorama programme (18 Aug) making similar and compelling arguments to support the way that NICE makes its decisions.

However, while we understand the implications of a resource-limited NHS, our concern about NICE remains; that the way in which it considers the impact of a condition and its treatment is sometimes at odds with the impact experienced by the individual. NICE appraisals need to ensure that cost-effectiveness and calculation of quality-adjusted life years (QALYs) take full account of the patent's perspective.

In the news…

Click on the links below to read

- Positive thinkers 'avoid cancer'
- Drug firms call for debate on access
- UK health partnership deal a boon for new drug research
- Gaps in NHS diabetes care remain
- Harm from prescription drugs likely to grow
- Running can slow 'ageing process'
- Watchdog chair to get tough on obeying NICE rules

Forthcoming events

7-11 September 2008
EASD 44th Annual Meeting:
Rome, Italy

9-12 September 2008
European Health Psychology Society / BPS Division of Health Psychology Annual Conference:
University Of Bath, UK

20-23 October 2008
DIA 2nd Annual Clinical Forum
Ljubljana, Slovenia

22-25 October 2008
ISOQoL 15th Scientific Meeting
Montevideo, Uruguay

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