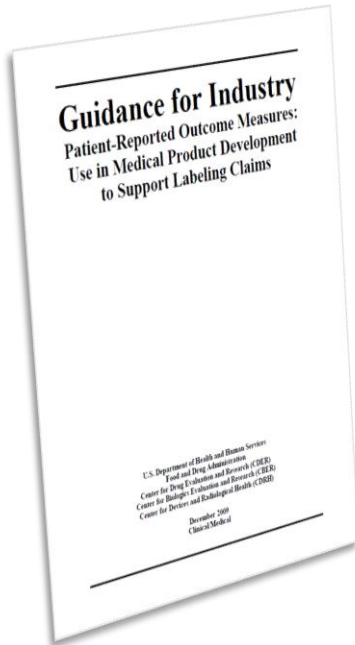


Good Questions

Issue 37

January 2010



The FDA final PRO guidance: raising the stakes or improving the odds?

SPECIAL ISSUE: Reflections on the FDA's Guidance for Industry (9 December 2009) Patient-Reported Outcome (PRO) measures: use in medical product development to support labeling claims

The recent release of the US Food and Drug Administration (FDA) guidance on the use of PRO measures to support labelling claims¹ has been eagerly anticipated since the publication of the draft guidance². In the past four years, there has been much speculation about the meaning and implications of the FDA's 'current thinking' about the development and use of PRO measures (PROMs). The draft guidance was designed to offer a set of guiding principles to those conducting and supporting industry-sponsored clinical trials, to enable industry to engage with the regulatory authority in a dialogue about the appropriate use of PROs to evaluate medicinal products. However, while the draft guidance was largely welcomed as a means of encouraging the adoption of scientific standards, it generated more questions than answers about the nature of PRO research and the level of evidence required to demonstrate good scientific practice.

Since the release of the draft guidance, the number of successful label claims has fallen (compared with the preceding five years)³, indicative of the increased challenges faced

by pharmaceutical companies wanting to demonstrate the benefits of their products from the patient perspective.

Furthermore, successful claims have been largely symptom-based, again providing compelling evidence of the difficulty (or perceived difficulty) of securing a claim based on more contentious (though, arguably, more patient-centred) concepts such as psychological well-being, treatment satisfaction or health-related quality of life. Thus, while the draft guidance raised the profile and value of PROs among industry, it also positioned many hurdles that smaller pharmaceutical companies might struggle to overcome. So, does the release of the final guidance last month mean that the FDA is now placing its cards on the table or is it just raising the stakes?

What are the main changes to the guidance?

The delay in the release of the guidance has been due, in no small part, to the number of concerns raised by the draft guidance amongst key stakeholders.

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**Wishing all our readers, clients
and collaborators
a happy, healthy and peaceful
New Year
from everyone at
AHP Research**



...because good questions outrank easy answers...

Is the FDA finally laying its cards on the table or raising the stakes even higher?

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More than 50 individual responses were received from various academics, health professionals and policy makers in addition to pharma industry and clinical research organisation (CRO) representatives¹. Thus, it should be no surprise that the focus and emphasis of the guidance has shifted somewhat from the FDA's original stance. As it is beyond the remit of this paper to provide a line-by-line account of the changes between the draft and final guidance, the following serves to highlight some key issues.

Overall focus

The guidance describes how the FDA "reviews and evaluates existing, modified or newly created PRO instruments used to support claims in approved medical product labelling"^{1, p1} and goes on to state that a PRO instrument is a "means to capture PRO data used to measure treatment benefit or risk in medical product clinical trials"^{1, p1}. In these short introductory statements, the FDA has made two important changes.

First, the focus has moved from describing how the FDA evaluates "PRO instruments" to acknowledging the different approaches that may be needed with regard to reviewing the suitability of "existing, modified or newly created" instruments. Second, the guidance now takes a more balanced perspective, acknowledging that PRO data can be used to measure treatment risk (e.g. side effects, inconvenience) as well as benefit; risk was not previously mentioned.

Endpoint models and conceptual frameworks

Four years ago, the draft guidance introduced the language of endpoint models, conceptual models and conceptual frameworks and this was met largely with confusion and much speculation about the nature of these overlapping ideas. The new guidance eliminates conceptual models. It begins with a discussion of the use of endpoint models, which serve to emphasise the importance of matching chosen outcome measures to specific treatment objectives, i.e. defining "the role a PRO endpoint is

intended to play in the clinical trial"^{1, p3}. The conceptual framework of a PRO instrument "explicitly defines the concepts measured by the instrument in a diagram that presents a description of the relationships between items, domain (subconcepts) and concepts measured"^{1, p7}. Diagrams and further explanations are provided to improve clarity. Endpoint models and conceptual frameworks may be relatively new terminology but, essentially, they just represent good practice in ensuring the appropriate selection of PRO instruments.

Content validity

Content validity is "the extent to which the instrument measures the concept of interest"^{1, p12}. This aspect of an instrument's properties is highlighted as fundamentally important (it now has its own dedicated section) with the following significant statement: "evidence of other types of validity ... or reliability ... will not overcome problems with content validity because we evaluate instrument adequacy to measure the concept represented by the labelling claim"^{1, p12}. Sponsors are encouraged to support the adequacy of content validity by documenting how items were generated. The guidance states that the FDA "cannot provide recommendations for the number or size of the individual patient interviews or focus groups for establishing content validity ... generally, the number of patients is not as critical as interview quality and patient diversity"^{1, p13}, confirming the importance of sound qualitative research to inform instrument design.

Importantly, the FDA acknowledges from the outset that "PRO instrument development is an iterative process and [they] recognize there is no single correct way to develop a PRO instrument. Different strategies and methods can be used to address FDA review issues"^{1, p2}. Previously, the standards for instrument development suggested by the draft guidance may have been very difficult

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Health Awareness - dates for your diary

- Health month
- Hypoparathyroidism World Awareness Day: 5 Jan
- Cancertalk Week: 18-22 Jan
- Food Allergy and Food Intolerance Week: 25-29 Jan
- Leprosy Week: 25-31 Jan

Is the FDA finally laying its cards on the table or raising the stakes even higher?

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to achieve, particularly for those developed and validated pre-guidance. Now, the FDA makes explicit that existing instruments with a less than rigorous development history can be considered if "new qualitative work similar to that conducted when developing a new instrument can provide documentation of content validity"^{1, p13}.

The guidance has expanded significantly in this area, detailing how content validity can be demonstrated and documented. The assessment of content validity includes detailed examination not only of item generation and patient understanding of items and response options but also the appropriateness (to the patient group) of: the data collection method and administration mode; recall period; instrument format, instructions and training. The guidance also presents criteria against which content validity and respondent and administrator burden will be assessed. In relation to the recall period, the FDA continues to promote use of items with "short recall periods or items that ask patients to describe their current or recent state"^{1, p14}, asserting that instruments that require recall over a longer period (i.e. relying on memory) may threaten content validity.

Making the headlines

- ['Risky donor' kidney transplants prove successful](#)
- [Many starting school 'overweight'](#)
- [Chief Medical Officer Liam Donaldson resigns](#)
- [People who look young for their age 'live longer'](#)
- [Body clock link to heart disease](#)
- [Free smoking quit kits launched](#)
- [Music therapy for tinnitus hope](#)
- [US Senate passes key health bill](#)
- [Negative emotions outweigh intent to exercise at health clubs](#)

There have also been noteworthy changes to the emphasis and focus of the guidance in the following areas:

- Measurement properties
- Instrument modification
- Proxy measures
- Interpretation of PRO data
- PRO evidence dossier

For full details of these changes (in an expanded version of this article), please [contact us](#).

Conclusions

The guidance has changed in many ways (in response to the concerns and issues raised by numerous stakeholders) to provide clearer messages for researchers, which emphasise the sound scientific principles by which PRO instruments should be developed and implemented. By emphasising good science but also providing greater clarity about the evidence required for FDA review, we believe that the FDA has simultaneously raised the stakes and improved the odds of securing label claims based on PROs.

The guidance emphasises the need to formulate a clear strategy for the inclusion of PROs in clinical trial programmes, just as for other clinical endpoints. Interestingly, it is widely speculated that the FDA will soon be turning its attention to the validity / reliability of clinician-reported outcomes, a decision which may not be popular but certainly promises to bring greater scientific rigour to outcomes that are often (ill-advisedly) regarded as more robust than PROs.

Most importantly, the guidance gives pre-eminence to content validity when evaluating the suitability of a PRO instrument and emphasises the importance of specifying the role of the PRO instrument amongst the range of trial / research endpoints. These are fundamental practices that can and should be adopted by any researcher or clinician and serve to ensure that outcomes reported from the patient perspective are both robust and meaningful.

References

1. US Department of Health and Human Services FDA CDER, CBER, CDRH. [Guidance for Industry: Patient-Reported Outcome \(PRO\) Measures: Use in medical product development to support labeling claims](#). 9 Dec 2009.
2. US Department of Health and Human Services FDA CDER, CBER, CDRH. [Guidance for Industry: Patient Report Outcome \(PRO\) Measures: Use in clinical medical product development to support labelling claims: draft guidance](#). HQLO 2006; 4(79).
3. Caron M et al. Recent Trends in the Inclusion of Patient-Reported Outcome (PRO) Data in Approved Drugs Labeling by the FDA and EMEA. PRO Newsletter 2008; 40.



The 'Wheel of Life' – a novel method for establishing the content validity of HRQoL measures

The FDA's final guidance on the use of patient-reported outcome (PRO) measures to support labelling claims places firm emphasis on the importance of content validity. At AHP Research, we have long been concerned about inappropriate use and interpretation of PRO measures¹ (see *Good Questions, May 2009*) and are committed to ensuring that our design of new PRO measures uses appropriate methods to ensure good content validity (see *Good Questions, April 2009*).

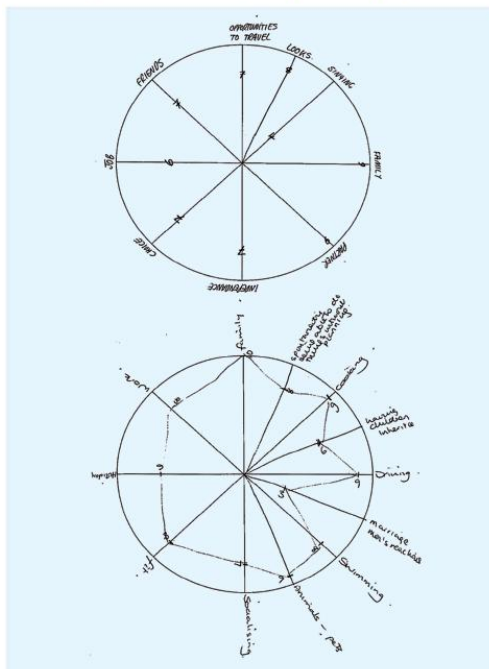
Content validity is "the extent to which the instrument measures the concept of interest. [It] is supported by evidence from qualitative studies that the items and domains of an instrument are appropriate and comprehensive relative to its intended measurement concept, population and use"^{2(p12)}. Many so-called health-related quality of life (HRQoL) measures include domains such as health, mobility and pain, which do not feature heavily in patient reports when asked "how does X condition affect your quality of life?"³.

At the recent UK Society for Behavioural Medicine (Southampton, 14-15 Dec 2009), Jane Speight (AHP Research) and Alison Woodcock (Royal Holloway, University of London) presented the 'Wheel of Life'. It is derived from an established life-coaching technique (e.g. Mindtools⁴) but has not been used previously in HRQoL research. We used it in a qualitative study designed to explore the impact of islet / pancreas transplant on quality of life in people with Type 1 diabetes⁵.

References

- Speight J et al (2009) Not all roads lead to Rome - a review of quality of life measurement in adults with diabetes. *Diab Med*, 26, 315-327
- US Department of Health and Human Services FDA CDER, CBER, CDRH. *Guidance for Industry: Patient-Reported Outcome Measures: Use in medical product development to support labeling claims*. 9 Dec 2009
- McGee H et al (1991) The SEIQoL in a healthy and gastroenterology population. *Psychol Med* 21:749-59
- www.mindtools.com/pages/article/newHTE93.htm
- Speight et al (2009) Expectations and experiences of transplant: a qualitative study of people with Type 1 diabetes undergoing pancreatic islet transplantation. *Diab Med* 24(Suppl. 1): 189.

Figure 1. Two examples of the *Wheel of Life* created by interviewees (both pre-transplant)



We are confident that the *Wheel of Life* will be useful not only in questionnaire design but also for demonstrating the content validity of existing HRQoL questionnaires in new conditions. For further information or a copy of the full poster presented at UKSBM, please [contact us](#).

Table 2. Descriptions* of impact of diabetes / transplant on elements of life facilitated by *Wheel of Life*

Spoke label (element of life)	Participant's comments
Job	[Pre-transplant:] quite a lot of the time I used to have really bad hypos, and ... it did cause problems, so I was basically taken out of that areaxx
Exercise	I recently joined a local gym... Before the transplant [I] wouldn't have dreamed of going ... I was never well; I never felt well
Husband	He used to come home and see me quite unwell and ... had to bring me out the comas ... and couldn't cope with it ... it tends to cause arguments and ... I didn't listen to him ... when I was hypo, 'cos it just goes out your head ... And it upset him. [Post-transplant:] If he wants to go away for week-end, it doesn't stop us ... He doesn't have to worry about me
Mood	Before the transplant I was quite depressed ... [being on the transplant list] made me feel good
Dogs	I like the exercise and I love my dogs ... the spaniel ... knew every time that I was hypo. Many are the times I was, you know, stumbling back here, hypo ... and it does upset them
Friends	Because people were worried about me ... but not now
Family	My sister thinks it's affected her ... 'cos I used to be 'very special' when I was younger... You know what I mean? But she thought basically I was being spoilt. And that stayed with her... until recently
Driving	I don't have to worry about going on long journeys; I'm more confident in driving and stuff... before the transplant, I wouldn't go anywhere apart from work and back, or to the local shops that I know: I would never venture out anywhere

*all comments from one participant (female, post-transplant)

Forthcoming events

7-10 April 2010

Society for Behavioural Medicine (SBM) 31st Annual Meeting

Seattle, USA

15-19 May 2010

International Society for Pharmacoeconomics and Outcomes Research (ISPOR) 15th Annual International Meeting

Atlanta, USA

4-7 August 2010

International Congress of Behavioural Medicine (ICBM) 11th Annual Meeting

Washington DC, USA

Abstract deadline: 15 Jan