

Do we need systematic reviews to support use of patient-reported outcomes (PRO) measures in clinical trials?

The following article is an adaptation of:

Smith D, Reaney MD and Speight J. Conducting literature reviews to support the use of patient-reported outcomes (PRO) measures in clinical trials – the benefits of a systematic search strategy. *ISPOR Connections*, July / August 2009, 4-6.



Systematic reviews are regarded as one of the strongest forms of evidence (second only to meta-analysis). However, a recent review of 300 systematic reviews found that not all systematic reviews are equally reliable¹. If designed and conducted appropriately, systematic reviews can prove invaluable to clinicians, guideline developers, regulatory agencies, grant awarding bodies and research ethics boards. Their use can inform clinical practice, national guidelines and justification for new research bids.

Few pharmaceutical-led clinical programmes begin with a review of the literature but in recent years, systematic reviews have become increasingly important in patient-reported outcomes (PRO) research. The US Food and Drug Administration (FDA) draft guidance on the use of PROs in medical product development² offers the opportunity for pharmaceutical companies to make labelling claims based on PRO assessments. However, high-level evidence is required to ensure that PRO data are meaningful and that the best available PRO instruments are used to measure a preferred endpoint. Systematic identification of condition-specific issues and the appraisal of PRO endpoints and existing instruments are therefore essential to:

- Determine burden of illness
- Identify potentially relevant PRO instruments
- Critically review relevant PRO

instruments to determine the most appropriate for the purpose

- Inform the design or adaptation of PRO instruments

The FDA draft guidance has, thus, given renewed weight to the role of the systematic literature review as the cornerstone of the clinical programme. The identification (and critical appraisal) of previously developed PRO questionnaires purporting to measure selected endpoints is one of the fundamental questions on which all PRO measurement strategies need to be built to maximise the chance of having data suitable for consideration in a product labelling claim.

However, the principles of this regulatory guidance (and that provided in 2005 by the CHMP of the EMEA³) do not end at the achievement of a label claim, but apply equally to post-marketing studies. We also note that such principles of good practice extend well beyond pharmaceutical industry trials and observational studies. Indeed, as we noted when conducting our recent review of quality of life measurement in diabetes⁴, few published studies provide a detailed rationale for the PRO instruments used. While some provide a rationale for the concept under investigation, far less show evidence that they have scrutinised all possible measures and provided an authoritative and objective justification for the PRO measures selected.

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In the news



▪ [Men with angina “at greater risk”](#)

Men with angina (a type of chest pain caused by insufficient supply of blood to the heart muscle) are twice as likely to have a heart attack and almost three times as likely to suffer a heart disease-related death as women. Published in the *British Medical Journal* by researchers at the National University of Ireland, Galway, these findings are based on a study of 1,785 patients in Scotland, diagnosed with angina from January 1998 to December 2001, whose progress was tracked for five years.

Being male, older and a smoker was associated with increased risk of a heart attack, while the same risk factors along with obesity were also associated with a higher risk of dying from heart disease. It is estimated that 4.8% of men and 3.4% of women in England have angina, with higher rates in Scotland (6.6% of men; 5.6% of women). The greater incidence of angina in men along with confirmation that risk of adverse outcomes is also higher in men is likely to lead to a call for more research into the reasons for this gender gap. This research also provides further confirmation of the importance of modifiable lifestyle factors and behavioural choices.

▪ [One third of doctors do not want swine flu vaccination](#)



A recent survey conducted by Healthcare Republic for *GP* newspaper has found that almost 3 in 10 GPs said that they would not have the swine flu vaccine, with the same number again, 29% unsure whether they would or not. Of the 216 GPs surveyed, more than 70% indicated their concern that there had not been sufficient trials of the vaccine. In a separate survey for *Pulse* magazine, 49% of 115 doctors said they would reject a vaccine with 10% undecided.

More than two thirds of those who would reject a vaccine believe the jabs have not been tested enough and most believe swine flu has been so mild in the majority of cases that a vaccine is not needed.

It seems that GPs' health beliefs are

Making the headlines

- [A Brief Behavioral Intervention Can Reduce Depression in Stroke Survivors](#)
- [Raising NHS staff wellbeing can ‘save trusts millions’](#)
- [Fewer smokers quit in past year](#)
- [Health secretary urges GPs to be “creative” in prescribing exercise](#)
- [High blood pressure linked to cognitive impairment](#)
- [Ovarian cancer is ‘being missed’](#)
- [Marriage breakdown affects cancer survival chances](#)
- [People “get happier as they age”](#)

Health Awareness

- dates for your diary

- [Pregnancy health month](#)
- [National Eczema Week: 12 – 19 Sept](#)
- [World Lymphoma Day: 15 Sept](#)
- [International Ataxia Day: 25 Sept](#)
- [World Heart Day: 27 Sept](#)
- [Rural Health Week: 27 Sept – 3 Oct](#)



influencing their decisions regarding their own health protection (and, indirectly, that of their patients and families). Another piece of research, published in *Emerging Health Trends*, found that parents and health workers refused to get immunised or vaccinate their children against swine flu. Parents known to favour alternative medicine were particularly opposed to vaccines.

The UK government is now fast-tracking 14 scientific projects, at an estimated cost of £2.25m, to understand the pandemic.



In the Journals

Perceived risk of medicine side effects: the effect of presenting risk information

- 1** Research into the provision of patient information has demonstrated that, under certain circumstances, patients overestimate the risks of medicine side effects.
- 2** Two experiments conducted with users of the Cancer Research UK patient information website investigated the effectiveness of presenting risk information in different forms about medicine side-effects.
- 3** In both experiments, participants were allocated randomly to one of three conditions for representing risk information:
 - 'natural frequency', e.g. 'x people in 10'
 - percentages, e.g. 'x%'
 - verbal description, e.g. 'common'
- 4** In experiment 1, 148 participants imagined taking a chemotherapy drug (Taxol®) and were asked to estimate the risks of two side-effects. In experiment 2, 137 participants estimated the risks of three side-effects occurring with use of the painkiller, ibuprofen.
- 5** In both experiments, verbal descriptions led to significantly higher estimates of risk compared to the other two formats, with some evidence that natural frequencies led to more accurate estimates than percentages.
- 6** These findings add weight to the growing body of research highlighting the deficiencies in using verbal descriptions of side-effect risk alone.

Knapp P et al (2009) Perceived risk of medicine side effects in users of a patient information website: a study of the use of verbal descriptors, percentages and natural frequencies. *Brit J Health Psychol*, 14(3); 579-594.

Do we need systematic reviews to support use of PRO measures...?

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While many aspects of the FDA's draft guidance are detailed and in some instances somewhat prescriptive, the messages regarding the rigour required of this most fundamental aspect of the PRO measurement strategy are less clear. Whilst the validity of the selected PRO instrument is rightly questioned by the FDA's draft guidance, the validity of the literature review that informs its selection is not. Systematic reviews are scientific exercises, requiring the same rigour as other aspects of research, yet current methods used to conduct so-called "systematic reviews" remain variable, meaning that the quality and comparability of systematic reviews is not assured.

A systematic review addresses a clearly defined research question through use of a clear and comprehensive methodology to identify, select and critically appraise relevant research studies, and to synthesise data from these research studies. In using a rigorous methodology, systematic reviews aim to minimise bias associated with study selection, identify all relevant research studies from the sources searched and be transparent in their methods and conclusions. The seven stages of a systematic review are detailed in Figure 1 (below) and will be expanded upon in next month's *Good Questions*.

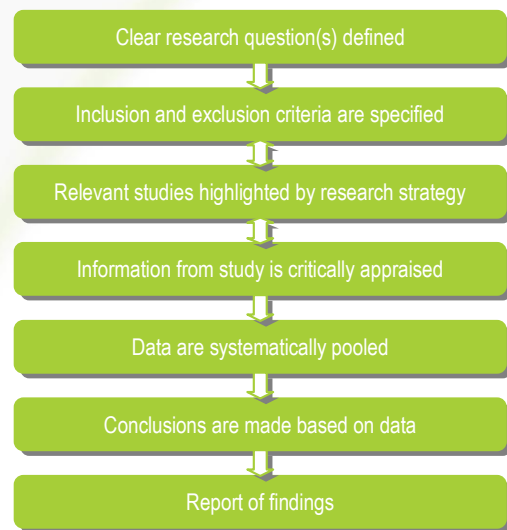


Figure 1. Stages of a systematic review

"few published studies provide a detailed rationale for the PRO instruments used"

References

1. Moher D et al. Epidemiology and reporting characteristics of systematic reviews. *PLoS Med* 2007; 4:e78.
2. FDA (2006) Guidance for Industry: patient-reported outcome measures: use in medical product development to support labelling claims: draft guidance. HQLO doi: 1186/1477-7535-4-79.
3. CHMP (2005) Reflection paper on the regulatory guidance for the use of health-related quality of life (HRQL) measures in the evaluation of medicinal products. Retrieved from: <http://www.emea.europa.eu/pdfs/human/ewp/13939104en.pdf>
4. Speight J et al (2009) Not all roads lead to Rome – a review of quality of life measurement in adults with diabetes. *Diabetic Medicine*, 26: 315-327.

Future issues – what would you like to read about?

Every now and then, we like to include contributions from researchers and clinicians who may have a different perspective or special interest to share. In the past, we have featured articles by guest authors, including Prof Peter Beresford (personal health budgets), Keith Wenzel (electronic PROs) and Prof Robert West (motivation).

If you would like to contribute to a future issue, nominate someone to offer an article or simply suggest a topic for inclusion, please [contact us](#). We look forward to hearing from you.



New journal launch: 'Health Outcomes Research in Medicine'



'Health Outcomes Research in Medicine' ([HORM](#)) is a new outcomes research journal due to be launched by Elsevier this Autumn.

The aim of the journal is to encourage and disseminate three basic principles:

- 1) the need for evidence for effective patient care
- 2) critical evaluation of that evidence
- 3) incorporating clinical judgment and patient reported outcomes (PROs) and preferences into decision-making regarding treatment and treatment efficacy

Like existing journals in this field, such as Quality of Life Research, HQLO, the Patient and Value in Health, HORM intends to publish articles involving the development, cultural adaptation and/or validation of PRO measures developed for general use in clinical practice or clinical trials. In addition, HORM intends to publish articles that provide an evidence base (in terms of clinical outcomes or PROs) for the allocation of scarce resources.

HORM will publish peer-reviewed papers of interest to a wide-ranging readership of clinicians, health researchers and policy makers. It is currently inviting the following types of papers:

- Original research and clinical trials
- Point/counterpoint debates
- Comprehensive reviews (of theory, methodology, and study findings in special areas of health services research);

systematic literature reviews and meta-analyses

- Commentaries
- Editorials

In summary, the journal is intended to be a medium for discussion and debate about the principles and substance of health outcomes research and how to improve patient outcomes. We hope that, in time, this new journal will be as influential and widely read as Health and Quality of Life Outcomes (see below).



What an impact!

We are pleased to report that the open access journal 'Health and Quality of Life Outcomes' ([HQLO](#)) has recently received its first official impact factor of 3.20. It is now ranked 4th of 62 in the field of healthcare sciences and services in the Journal Citation Report.

This is great news for a journal that was first published a little over six years ago when 'open access' was a relatively new concept in publishing.

On average, HQLO now publishes ten articles per month and continues to offer rapid dissemination of reviews and empirical research focusing on issues related to health, quality of life and other patient-reported outcomes.

Forthcoming events

9-11 Sept 2009

BPS Division of Health Psychology

Aston University, UK

23-26 Sept 2009

European Health Psychology Society

Pisa, Italy

9-11 Oct 2009

Why men die early and suffer more: 6th Biennial World Congress on Men's Health and Gender (WCMH)

Vienna, Austria

24-27 Oct 2009

ISPOR 12th Annual European Congress

Paris, France

28-31 Oct 2009

ISOQoL 16th Annual Conference

New Orleans, USA