Ensuring the successful use of patient-reported outcomes questionnaires in multinational clinical trials.

Practical Measures

Mary C. Gawlicki

The increasing use of patient-reported outcomes questionnaires (PROs) in multinational clinical trials requires that clinical trial managers and health economics and outcomes research (HEOR) practitioners be able to navigate often murky waters in order to successfully pass the scrutiny of regulatory authorities. Sponsors now routinely run clinical trials in emerging markets such as India and Africa and may require validated translations in up to 100 languages. While creating or procuring properly validated translations is an enormous task in and of itself, the challenges do not end there. Current technology is quickly moving from paper administration of PROs to electronic administration and, in so doing, inserts yet another wrinkle in the already complicated process. This article provides practical steps for eliminating potential confusion and streamlining the process of including PROs in multinational clinical trials.

Planning

Three elements are critical to the successful planning for the use of PROs in any clinical trial:

- Instrument selection
- Location of investigational sites
- Method of administration

While the PRO instruments selected for a trial are established during the study design phase, investigational sites often change over the course of the trial. Similarly, the method of administration may not be finalized at the outset. Complications arising as a result of these changes can be minimized by using several guidelines.

Language selection. Once a preliminary list of countries where the trial will be conducted is available, language selection should begin. The location of probable sites within each target country should first be evaluated to narrow the list of language/country combinations to be linguistically validated. As noted in Wilde et al.,[1] several criteria are useful in assessing which languages to prepare for countries where multiple local languages exist. For example, although there are 18 local languages in India, unless there are investigational sites in Punjabi- or Urdu-speaking regions, translations in those languages likely need not be developed. However, in countries where there are numerous speakers of an unofficial language of the country (e.g., Spanish in the United States), it is usually prudent to assume that translations in the unofficial language will be required.

Similarly, as noted in Wilde et al.[1] and Eremenco et al.,[2] the sponsor should analyze how many country-specific versions of the same language should be created. Considerations such as developer requirements, cultural similarity between countries, and whether adaptation of an existing version is possible should be weighed prior to developing additional versions of the instrument.

Availability of validated translations. With language/country list in hand, research must be conducted to determine if validated translations of the instrument exist in the language/country combinations needed. While some resources exist such as the websites www.PROQOLID.org, www.euroqol.org, www.dermatology.org.uk/quality/dlqi/qual-

ity-dlqi.html, and www.qualitymetric.com, these listings are not comprehensive and may not indicate the methods used to create the translations. In light of the final 2009 FDA Guidance on Patient-Reported Outcomes, the sponsor should be able to demonstrate that sufficient care was taken to ensure the validity of the translations.[3] Therefore, it is essential that translations obtained from developers be accompanied by certifications detailing the methodology used to create them. Any instrument without this evidence will need to be revalidated to ensure agency approval. As a result of the lack of a common, up-to-date database of available, properly validated translations, anyone responsible for the conduct of a clinical trial should plan sufficient time to research this issue.

Method of administration. In today's fast-paced clinical trial environment it is not unusual for clinical trial teams to finalize a decision to use ePRO administration rather than paper administration after translations of the PRO instruments have been initiated. Failure to adequately research and finalize the ePRO/no ePRO decision may present several challenges later in the process. Among the possible problems that may result from a failure to plan this early in the process are:

- Discovering that a cross-culturally adapted instrument requires usability testing.[4]
- Learning that existing translations are worded for paper not ePRO or IVRS administration.
- Selecting an inappropriate ePRO tool for the target language (e.g., Indian languages that may present font problems on a PDA).

Ensuring that the ePRO decision is made early will reduce the probability of serious issues arising later. Encountering any of the problems listed above will dramatically affect trial timelines.

Summary

Clinical trial managers and HEOR specialists should be mindful of several issues when planning a multinational trial involving PROs. Procuring appropriately validated translations for use in a trial can be a time-consuming and complex endeavor. Successful execution requires both planning and research. If newly validated translations are required, it is important to establish which languages to produce and when to produce multiple versions of the same language. Finally, where possible, determining the method of administration before initiating the translations can save precious time, reduce costs, and prevent regulatory surprises.

References

1. D. Wild, et al. "Multinational Trials—Recommendations on the Translations Required, Approaches to Using the Same Languages in Different Countries, and the Approaches to Support Pooling the Data: The ISPOR Patient-Reported Outcomes Translation and Linguistic Validation Good Research Practices Task Force Report," *Value in Health,* 12 (4) 430-440 (2009).
2. S. L. Eremenco, et al., "Methods for Addressing the Use of PRO Instruments in the Same Language for Different Countries: Best Practice Guidelines for Decision-Making and Translation or Adaptation," Presented at the International Society for Pharmacoeconomics and Outcomes Research 11th Annual European Congress, Athens, Greece, November 8–11, 2008.
3. Food and Drug Administration, *Guidance for Industry Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims,* (FDA, Rockville, MD, 2009).
4. S. J. Coons, et al., "Recommendations on Evidence Needed to Support Measurement Equivalence between Electronic and Paper-Based Patient-Reported Outcome (PRO) Measures: ISPOR ePRO Good Research Practices Task Force Report," *Value in Health,* 12 (4) 419-429 (2009).

Mary C. Gawlicki, *MBA, is President of Corporate Translations, Inc., East Hartford, CT, www.corptransinc.com.*