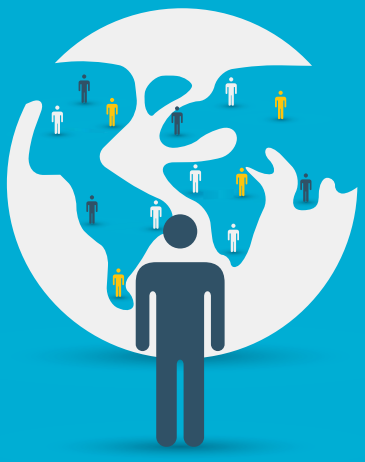

Logistical Considerations for Integrating Patient-Reported Outcomes in Multiregional Clinical Trials

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Patient-reported outcomes (PROs) are used increasingly in clinical trials for several purposes, including demonstrating efficacy as a primary endpoint and providing key data useful for product differentiation. Value propositions based on PROs, especially when included as nonprimary endpoints, provide data beyond the traditional efficacy and safety endpoints, and capture the patients' voice in drug development.

PRO is an umbrella term used to describe outcomes collected directly from the patient without interpretation by clinicians or others.[1–3] PRO data are collected via standardized questionnaires (also called instruments, scales, diaries, or checklists) designed to measure an explicit concept (construct) such as symptoms, activity limitations, and health status or health-related quality of life.

These PRO measures (PROMs) may include simple questions to measure the frequency (e.g., seizure rates in epilepsy) or severity (e.g., joint pain in arthritis) of a symptom.[4,5] More complex, multidimensional questionnaires are also used to measure health status in clinical trials. These include generic tools, such as the Short Form–36 (SF-36) Health Survey, which can be used across various disease areas, or symptom- and disease-specific measures that evaluate concepts important to patients experiencing the condition of interest.

A range of methodological issues must be considered to ensure the collection of high-quality data necessary for the various stakeholders for this information. Foremost, PROMs must be demonstrated to be both valid and reliable within the specific context of use.[6] In 2009, the U.S. Food and Drug Administration (FDA) formalized a set of evidentiary standards for using PROMs to support product label claims.[1]

Compared to other parameters captured in clinical trials, two aspects are unique to PRO data:

- PROs must be provided in the language most familiar to the patient. Therefore, appropriately translated and cross-culturally adapted PROMs must be used in clinical trials.[7]
- Unlike other assessments in typical clinical trials that can be queried at a later date, data from PROMs that capture how patients feel and function at specific times cannot be queried retrospectively.

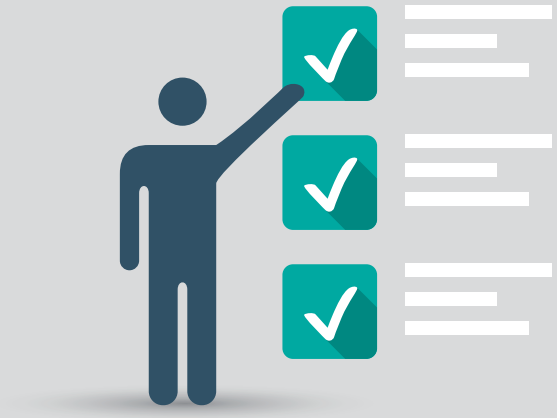
The combination of these two aspects with the increased number of countries participating in clinical trials[8] has led to a need for special attention to the logistical issues of integrating PROMs into studies.

This manuscript highlights some of the key logistical challenges of integrating PROMs in multiregional clinical trials (MRCTs).

INTERNAL RESOURCE ALLOCATION

The resources required to integrate PROMs in clinical trials cannot be underestimated. When there are "off-the-shelf" existing PROMs fit for a purpose, typical activities require obtaining appropriately validated PROMs, ensuring the availability of appropriately cross-culturally adapted and translated PROMs, implementing the most appropriate data-capture methods, preparing training materials for study coordinators and patients, and compiling briefing books to seek scientific advice from regulatory authorities.

Including PROMs in study protocols also requires contributions from many functions, such as development, data management, biostatistics, regulatory, and outcomes research. Research teams must know the breadth of these activities and ensure adequate time and resources in the clinical development plan.



There are no standard timelines for obtaining correct versions of PROMs and accompanying documentation (such as scoring algorithms), permission/license from authors or agencies, or appropriate language versions for a particular clinical trial.

If an existing PROM does not fit the required purpose, developing a novel PROM is an extensive process that can span two or more years. A gap analysis early in a drug's development is essential to assess the need for new PROMs and to initiate activities to ensure timely integration in clinical trials.

Internal resources are often secured when the intended PRO objective is specified as critical to a strategic document, such as the target product profile. Once integrated in the target product profile, one can be assured there is agreement among all functions and management that the PRO objective is essential to satisfying the product's regulatory needs, commercial needs, or both.

Agreement would be delineated when the PRO is the primary endpoint, but it may not when the PRO is a nonprimary endpoint, unless internal processes are in place to seek timely agreement. Lack of commitment from all parties often translates into suboptimal data, missed opportunities, and possibly additional cost.

PROTOCOL DETAILS

The study protocol describes the plan for conducting the clinical study and explains the purpose and function of the study and how to carry it out. It should include pertinent information, such as PRO objectives, assessment rationale, assessment schedule, modality of data capture, and analyses.

Study teams may fail to realize that many PROMs have distinct versions designated for various disease severity levels, with different recall periods, or for subpopulations, such as pediatrics. For example, there are two versions of the Asthma Quality-of-Life Questionnaire—an original published in 1991 and a standardized version, both available in self-administered versions, interviewer-assisted versions, and versions specific to children.

The protocol should include PROM names and corresponding versions or citations to assist in obtaining the correct PROM, and accompanying documents, such as scoring guides. Failure to do so may result in scoring of data intended for a PROM version that is incorrect for the study. Wherever possible, citations relating to validation, cultural adaptation, and analyses should also be included in the protocol.

Unique procedures should also be specified when data are expected from "special" populations (e.g., caregivers of elderly patients, parents of young children, or patients with movement disorders).

OBTAINING APPROPRIATE PROMS

Identifying appropriate PROMs depends on regulatory, commercial, and market access needs. This process is beyond the scope of this manuscript, but is covered elsewhere.[6,9]

Once a PROM has been identified for use, the following three criteria must be met before the PROM is integrated in a clinical study:

- The PROM must be the latest version available, although there may be exceptions if the drug development program requires maintaining consistency between studies. Details of versions and any requirements for specific PROMs are available from relevant websites (e.g., PROQoLID.org), publications, or the developers of the PROMs.
- All necessary validated language versions should be available at the time of submissions to institutional review boards/independent ethics committees (IRBs/IECs). These groups require the PROMs in local languages, so all required language versions of the questionnaires must be available at submission.
- Appropriate permission to use the measure must be granted, where applicable, and all relevant contractual matters between the developer (or the agent of the developer) and the sponsoring company must be signed off and archived.

There are no standard timelines for obtaining correct versions of PROMs and accompanying documentation (such as scoring algorithms), permission/license from authors or agencies, or appropriate language versions for a particular clinical trial. Therefore, study teams must account for these complexities during the planning stage—when writing the clinical development plan and target product profile—if PROMs are needed in a clinical trial.

The efficiency of integrating all necessary language versions of PROMs in an MRCT in a timely fashion depends on seamless interaction between the sponsoring company, the translation vendor, the ePRO vendor, and the PROM developer.

Data collection for PROMs requires special consideration, not only because patients are involved, but because the quality of data depends on the training and the predefined responsibilities of the study coordinator, investigator, and field monitor.

Study teams are advised to start activities, especially those relating to the acquisition and translation of the PROMs, well in advance (often months before the study starts), so they can be ready for submission to the relevant IRBs/IECs.

Members of study teams may be tempted to change various aspects of an existing PROM to suit their study. However, any changes to wording, sequence, response options, instructions, and administration method may invalidate a PROM. Permission must be obtained from the authors of the PROM (or translation) and documented before any changes are made. Changes may also warrant validation studies. These issues are important when a PROM developed for paper administration is considered for electronic data capture (ePRO).[10–12]

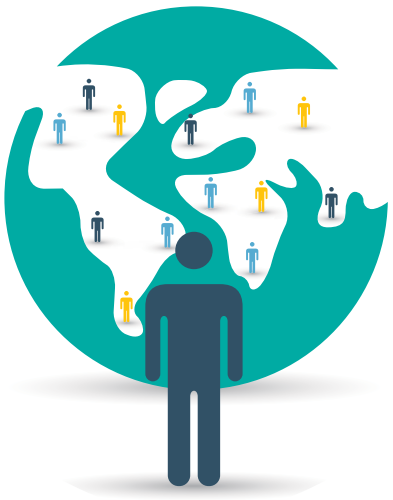
LANGUAGE VERSIONS

New translations of PROMs are often required for MRCTs. PROM translations, also called cultural adaptations, must adhere to strict methodology and may take six to nine months to develop.[7]

The PROM translations required for a specific clinical trial are governed not only by the official languages of the country, but also by the languages spoken by minority populations in that country. Knowledge of ethnic mix and the locations of study centers may also help identify language versions required.

Companies that provide translation services should also provide certificates of translation. Certificates for existing translations can be obtained from the authors of the instruments. Even if translations are available, the corresponding certificate of translations must also be available in time for IRB/IEC submissions.

An increasing number of IRBs and IECs now require certificates of translation and finalized patient-facing screenshots for PRO instruments (if ePRO is used) before studies are approved. IRBs and IECs are usually forgiving if certificates of validation are not available for instruments developed many years ago, but have been widely used and accepted. If certificates of translations are not available, study teams may consider retranslation.



RESOURCE MANAGEMENT

The efficiency of integrating all necessary language versions of PROMs in an MRCT in a timely fashion depends on seamless interaction between the sponsoring company, the translation vendor, the ePRO vendor, and the PROM developer. Since a typical study may include multiple PROMs, the roles, responsibilities, and lines of communication should be defined as early as possible following the completion of necessary legal obligations between all parties.

INVESTIGATOR MEETINGS

Investigator meetings and site initiation meetings are key opportunities to provide information and training materials for PROMs. A presentation should cover topics such as the purpose of the PROMs, the number of questions in each PROM, and the details of the response scales. A list of recommended topics is given in the sidebar.

Written instructions, such as training manuals or case report form completion guidelines, are strongly recommended, and archiving prerecorded trainings (e.g., on DVD) at the site may help refresh training or train new staff for longer trials. Documentation of this training should be included in the PRO evidence dossiers submitted to the regulatory agencies.

PREPARING THE SITE

Preparing the study sites is the key to successful study execution. Because field monitors are the main contacts in the participating sites, both the field monitors and clinical site staff must be informed and trained on the objectives, requirements, and methods of PRO data collection. The following actions are crucial:

- The center has received approval for IRB requirements.
- Appropriate steps have been taken to ensure study coordinators and investigators are trained for their duties and responsibilities before, during, and after data-collection activities.
- The site staff know that PROMs are integral to the study and not separate from the protocol. A person dedicated to the trial (e.g., study coordinator) should be designated as the person responsible for the administration of the PROM, and he/she should have the interpersonal skills necessary to assist patients without influencing their responses. Influencing patients' responses by interpreting the questions or by suggesting responses may introduce bias and invalidate the study results.
- Whenever PROMs are included as part of a trial design—especially in diseases relating to mental disorders or serious conditions such as cancer—patients may have a heightened expectation of access to support services. In disease areas where this may be a concern, study coordinators should identify a short list of social services, mental health, counseling, or pastoral resources

available to address patients' emotional needs. Study staff may also have the name and contact number for someone to call in case a patient becomes upset. For protocols using PROMs with especially sensitive questions, some IRBs require researchers to state how psychosocial distress will be identified and addressed.

- The site must agree on resources and guidelines for storage, protection, and access restriction of source documentation.

SITE TRAINING

The field monitor must be the key interface between the trial's sponsor and the site's staff during a trial. Although initial site training may be done at the investigator meetings, most interaction will occur between the field monitor, site coordinators, and investigators. Therefore, field monitors' acceptance of the importance of PRO assessments is crucial to ensuring that the correct message is transmitted to participating sites.

Data collection for PROMs requires special consideration, not only because patients are involved, but because the quality of data depends on the training and the predefined responsibilities of the study coordinator, investigator, and field monitor.

The training of study coordinators is essential for improving data quality, minimizing inconsistencies, and satisfying regulatory guidance.[1] Training considerations must include the possibility of inexperienced study staff administrating questionnaires and the burden on both staff and patients of administrating multiple questionnaires. Documentation of site and patient training is part of a PRO evidence dossier submission to support label claims, so care should be taken in documenting this training.

Field monitor and site personnel training should not be confined to investigator meetings or site initiation visits. Ongoing dialogue should be encouraged among site coordinators and field monitors, who may communicate issues or concerns directly to the study trial leader. Further actions to be considered are provided in the sidebar.

CONCLUSION

PROs are increasingly used in clinical trials to demonstrate efficacy and differentiate products. Unlike traditional efficacy and safety endpoints, a PRO strategy faces unique logistical challenges when implementing it at the study level.

The key to successful implementation of PROMs in MRCTs is anticipating the logistical considerations early in the process and having clearly defined roles and responsibilities for sponsors, PROM authors, translation companies, and ePRO companies.

Recommended Topics for Investigator Meetings When Using PROs

- ☑ Purpose of inclusion of each PROM
- ☑ Number of questions and time required to complete each PROM
- ☑ Details of response scales
- ☑ Dimensions covered (e.g., physical functioning, social functioning, etc.)
- ☑ Recall period related to the questions or dimensions
- ☑ Assessment schedule of each PROM by way of a schematic diagram of the study design highlighting the visits and order in which the PROMs will be administered
- ☑ Language versions of PROM for each participating country
- ☑ Aspects related to how the required materials (e.g., PROMs, ePRO devices, training materials, storage of devices) will be distributed to the study centers
- ☑ Ways of dealing with patients with special needs, such as visual impairment or movement disorders
- ☑ Responsibilities of the study coordinator and investigator before, during, and after the PROMs are completed

Recommendations for Study Site Training When PROs are Included

- ☑ All sites and field monitors should participate in training at the investigator meeting. Sites should communicate any changes in site coordinators to allow for communication of training materials to new personnel.
- ☑ A specific section of clinical trial newsletters should address any PRO-related issues.
- ☑ Positive feedback should be given to sites to encourage compliance and keep their focus on the PRO section of the protocol.
- ☑ A regular question-and-answer letter may be circulated by the study teams to site field monitors to ensure resolution of questions that arise.
- ☑ Site field monitors should address their questions directly to study leaders to ensure consistency of solutions.
- ☑ A feedback questionnaire may be collected from site coordinators and patients to obtain their comments on the PRO assessment process.
- ☑ Webinars or training modules should be offered to centers that join the study late.

References

1. U.S. Food and Drug Administration. 2009. Guidance for Industry: Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims. www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM193282.pdf
2. Acquadro C, Berzon R, Dubois D, Leidy NK, Marquis P, Revicki D, Rothman M. PRO Harmonization Group. Incorporating the patient's perspective into drug development and communication: an Ad Hoc Task Force report on the Patient-Reported Outcomes (PRO) Harmonization Group Meeting at the Food and Drug Administration, February 16, 2001. *Value Health* 2003;5:522–31.
3. Doward LC, McKenna SP. Defining patient-reported outcomes. *Value Health* 2004;September–October, 7 Suppl 1:S4–8.
4. Elger CE, Stefan H, Mann A, Narurkar M, Sun Y, Perdomo CA. 24-week multicenter, randomized, double-blind, parallel-group, dose-ranging study of rufinamide in adults and adolescents with inadequately controlled partial seizures. *Epi Res (Amsterdam)* 2010;88:255–63.
5. Dworkin RH, Turk DC, Peirce-Sandner S, Baron R, Bellamy N, Burke LB, et al. Research design considerations for confirmatory chronic pain clinical trials: IMMPACT recommendations. *Pain* 2010;149:177–93.
6. Patrick DL, Burke LB, Gwaltney CJ, Leidy NK, Martin ML, Molsen E, Ring L. Content validity—establishing and reporting the evidence in newly developed patient-reported outcomes (PRO) instruments for medical product evaluation: ISPOR PRO Good Research Practices Task Force Report: Part 1—eliciting concepts for a new PRO instrument. *Value Health* 2011;14(8):967–77.
7. Wild D, Eremenco S, Mear I, Martin M, Houchin C, Gawlicki M, et al. Multinational trials—recommendations on the translations required, approaches to using the same language 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 Health* 2009;12:430–40.
8. Thiers FA, Sinskey AJ, Berndt ER. Trends in the globalization of clinical trials. *Nature Rev Drug Disc* 2008;12(7):13–4.
9. Patrick DL, Burke LB, Gwaltney CJ, Leidy NK, Martin ML, Molsen E, Ring L. Content validity—establishing and reporting the evidence in newly developed patient-reported outcomes (PRO) instruments for medical product evaluation: ISPOR PRO Good Research Practices Task Force Report: Part 2—assessing respondent understanding. *Value Health* 2011:978–88.
10. Coons SJ, Gwaltney CJ, Hays RD, Lundy JJ, Sloan JA, Revicki DA, Lenderking WR, Cella D, Basch E. Recommendations on evidence needed to support equivalence between electronic and paper-based patient-reported outcome (PRO) measures: ISPOR ePRO Good Research Practices Task Force Report. *Value Health* 2009;June:419–29.
11. Stone AA, Shiffman S, Schwartz JE, et al. Patient non-compliance with paper diaries. *BMJ* 2002;324:1193–1194
12. Tiplady B. Electronic patient diaries and questionnaires—ePRO now delivering on promise? *Patient* 2010;3:179–183

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