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Review

Integration of patient-reported outcomes in multiregional confirmatory clinical trials

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Introduction: The increasing complexities of conducting multiregional trials and an evolving regulatory environment contribute to unprecedented new challenges for use of patient-reported outcome measures (PROMs)1 within clinical trials. This paper presents these challenges and potential solutions.

Methods: Real-world examples and situations are reviewed from an industry and patient-reported outcome (PRO)2 expert position.

Conclusions: An increase in the pursuit of new therapeutic targets, changes to the regulatory environment, and business pressures to expand clinical trials to more countries have significantly increased the complexity of confirmatory clinical studies that incorporate PROMs. Decisions to participate in collaborative efforts for endpoint development or proceed independently are made in the context of competing priorities of drug development timelines, drug differentiation strategies, the need for patient-related value messages, and the depth of a sponsor pipeline within specific disease areas. Study logistics are critically important; factors such as concept cultural relevancy, respondent literacy level, and quality of cross-cultural adaptation of PROMs must be evaluated when integrating into confirmatory clinical trials. Awareness of the issues relating to PROs in multiregional studies will enable companies to better plan studies and interpret results.

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1 Patient-reported outcome measures.
2 Patient-reported outcome.

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1. Introduction

Well-controlled clinical trials are the most effective means to identify safe and efficacious pharmaceutical treatments. Confirmatory clinical trials, or phase 3 trials, are intended to provide firm evidence for efficacy and safety claims. Clinical trial primary endpoints are mainly a combination of physiological and clinical response measures. However, in addition to these endpoints, patient reported outcomes (PROs) are often included. Patient direct report is central to the overall evaluation of drug effect to fully understand how a patient feels or functions in response to treatment. This understanding can be critical in assessing safety and efficacy and may provide important insight to generate patient-relevant information for pharmaceutical products [1].

PROs [3] are collected in an increasing number of clinical trials [2] via standardized questionnaires designed to measure an explicit concept (construct) such as symptoms, activity limitations, health status, HRQOL [4] or QOL [5]. These questionnaires, also called instruments, scales, diaries, checklists, or measures, are collectively referred to as PROMs [6]. For new products approved between 2006 and 2010, almost a quarter of treatment-benefit claims granted by the US FDA [7] were based on PROMs [3].

In the absence of objective markers of a disease, for instance, for symptoms of irritable bowel syndrome, migraine, or pain, treatment efficacy must be reported directly by the patient. In such instances, PROs will be the primary endpoints of confirmatory clinical trials. A recent review of PRO-related labels granted by the FDA between 2006 and 2010 showed that a PRO was the primary endpoint for 20 of the 28 products (71.4%) with at least one PRO claim [3].

A PRO may also be a key secondary endpoint, either independent of or closely associated with the primary endpoint. Regulators often require verification of a sponsor’s primary endpoint using a co-primary or secondary endpoint. For example, in Alzheimer’s disease, it is not sufficient to achieve improvement in the ADAS-Cog [9] without showing improvement in daily activity performance. In COPD, [10] showing improved lung function by FEV1 [11] is insufficient without evidence of improved physical activity and patient-reported symptoms.

3 Patient-reported outcomes.
4 Health-related quality of life.
5 Quality of life.
6 PRO measures.
7 United States.
8 Food and Drug Administration.
9 Alzheimer’s Disease Assessment Scale–Cognitive subscale.
10 Chronic obstructive pulmonary disease.
11 Forced expiratory volume in 1 s.

Additionally, regulators may request assessment of different aspects of the patient experience using PROs. The assessment of multiple impacts of SLE [12] has been suggested by both the FDA [4] and the EMA [5]. Both regulatory bodies recognize the implications of this debilitating disease and suggest, in addition to standardized clinical assessments of disease activity (such as the BILAG [14] or the SLEDAI [15]), the "use of patient-reported outcome instruments to measure all relevant and important SLE symptoms and patient-perceived abilities to function and perform daily activities" [4] and the assessment of quality of life via the Lupus QOL [5].

There are many challenges associated with the inclusion of PROMs in clinical trials. Some of the challenges are the following: identification of the concepts to measure, understanding that there are trials which may not be conducted in traditional markets because it may give rise to unexpected variation stemming from cultural influences impacting PROs; having timely access to cross-culturally adapted PROMs that can reliably capture patients’ view, ability to collect data at appropriate time points, and interpretation of the data.

Recently, there have been many changes in the environment within which the pharmaceutical industry operates. Whereas some of these changes have enabled the companies to better integrate PROMs in MRCTs [16] some changes have introduced new challenges that impact the integration of PROMs in clinical trials. This paper aims to discuss these challenges and provide potential strategies to address them.

2. Recent developments facing the pharmaceutical industry

There have been three main recent developments that affect the use of PROMs in the pharmaceutical industry: (1) changes in the regulatory environment; (2) the increasing number of new, emerging, or previously undiagnosed diseases that impact public health; and (3) the changing nature of MRCTs.

2.1. Changes in the regulatory environment

In the US, the FDA has formalized a set of evidence standards for PROMs to be used in clinical trials to support product labeling.
claims. PROMs must meet the requirements described in the FDA’s guidance for industry, Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims [6] and label claims must be supported by appropriately designed investigations using PROMs that have been demonstrated to measure the concept underlying the claim [7].

In contrast, the EMA has produced a Reflection Paper [5] to provide broad recommendations on the use of PROMs in clinical trials. Additionally, in 2008 the EMA developed a Biomarker’s Qualification program. This qualification program provides a formal mechanism for ratifying clinical trial endpoints, including new or existing PROMs [8]. The FDA also issued draft guidance in 2010 Guidance for Industry: Qualification Process for Drug Development Tools [9]. This draft guidance describes a new qualification process for drug development tools which include, among other things, biomarkers and PROs. To date neither program has qualified any new PROM to be used in clinical trials.

2.1.1. Collaborative efforts

To improve the efficiency of efforts to develop and validate PROMs that meet regulatory requirements, there are collaborative initiatives in both the US and Europe. These collaborations between industry, regulatory bodies, and academia are distinct departures from the traditional approach of a single sponsor developing a measure for a single, specific drug development program within the confines of the competitive environment and move PROM development into a precompetitive environment where stakeholders recognize the value of pooling resources and expertise to enable successful development of PROMs. These collaborations also include close involvement by regulators and focus on improving testing methods and processes to evaluate the safety and effectiveness of medical products.

In 2005, the FDA and the pharmaceutical industry together launched the CPI.17 The CPI is “FDA’s national strategy for transforming the way FDA-regulated medical products are developed, evaluated, and manufactured” [12]. Under the CPI, in collaboration with the FDA, an independent initiative called the PRO Consortium was formed in 2006 [10] with the aim of implementing the CPI efforts by creating collaborations among major regulatory agencies worldwide, the medical product industry, academic institutions, and patient advocacy organizations.

The primary aim of the PRO Consortium is to develop “qualified, publically available PRO instruments, and facilitate FDA review of medical products by standardizing PRO endpoints” [11]. The initial five PRO Consortium working group topics were chosen from a list of 26 diseases/conditions for which the FDA had received multiple requests for advice on how best to measure PRO endpoints in clinical trials [11]. There are now eight working groups currently seeking PROM qualification by the FDA.

An initiative similar to the CPI called the IMI18 was also launched in Europe in early 2008 by the European Federation of Pharmaceutical Industries and Associations and the European Commission. Whereas the goal of both the CPI and IMI initiatives is to improve efficiency in drug development, the impetus for the CPI initiative stems from regulatory concerns and the impetus for the IMI came from the need “to make the drug discovery and development process in Europe more efficient and to enhance Europe’s competitiveness in the pharmaceutical sector” [12]. At present, there is no organization in Europe similar to the US PRO Consortium. Any development of PROs within IMI is managed as part of the initiative specific to one of the following five disease areas: brain disorders, cancer, metabolic, infectious, and inflammatory diseases. Only one PROM is currently under development within the IMI initiatives and its focus is to understand the patients’ experience of COPD [13].

Both initiatives are similar in the sense that they encourage biopharmaceutical industry collaboration in the precompetitive environment to combat inefficiency, increasing costs, declining productivity, and escalating complexity of regulatory requirements. The governance of both initiatives is shared by public and private partnership [13,14].

The implication of collaboration efforts to the drug manufacturers is discussed later in this paper.

2.2. Increase in the number of new therapeutic targets

The biopharmaceutical industry faces challenges addressing the growing list of new or emerging diseases which are the target of current drug development. Many of these diseases, defined as “either new, previously unrecognized diseases that are appearing for the first time, or diseases which are known but which are increasing in incidence,” [15] have significant public health implications. Examples include age-related diseases such as sarcopenia, infectious diseases such as SARS19 or avian influenza, chronic diseases such as obesity, and under-researched diseases such as inclusion body myositis. Additionally, there is an increase in the number of medicinal products under development to treat rare diseases (orphan drugs) [7]. The expansion of drug development into new disease areas and the new regulatory and market access environments has led to the need for many new disease-specific PROMs. However the collaborative initiatives mentioned previously are unlikely to be able to meet the demands of the industry. The IMI initiative is specific to certain disease areas, and the activities of the PRO Consortium are very much based on “the capacity to manage and staff additional working groups” and based on “the level of interest from member firms and regulatory needs.” [11].

2.3. Increase in the number of countries participating in multiregional studies

Driven largely by the need to cut costs and improve recruitment efficiencies, an increasing number of clinical trials, especially confirmatory clinical trials, are moving from the US and Western Europe to emerging markets such as Eastern Europe, Latin America, and Asia. For example the average annual growth rate, based on data available in 2007, of the number of clinical trials carried out in China and Poland increased by 47% and 17%.

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17 Critical Path Initiative.
18 Innovative Medicine Initiative.
19 Severe acute respiratory syndrome.
3. Challenges of patient-reported outcomes in confirmatory clinical trials

Formulating a successful PRO strategy goes beyond identifying the appropriate construct for measurement. Selecting the most suitable instrument also requires consideration of key quality standards. A well-designed PROM can assess patients across a broad spectrum of disease severity. Conversely, poorly designed PROMs may be incapable of identifying treatment changes in the measured construct for very mild or very severe patients. PROs that are highly relevant to the patient group under study will maximize the quality of the data collected. Further discussions relating to the choice of PROMs are provided elsewhere in the literature [1,17–19].

On the basis of some of the recent developments discussed previously, the challenges facing researchers when PROMs are included in confirmatory clinical trials can be summarized under following four categories: (1) the impact of culture and literacy on PRO data; (2) complex study logistics when PROMs are included in MRCTs; (3) intensive internal resource allocation; and (4) regulatory dilemmas.

3.1. Impact of culture and literacy on PRO data

Whereas confirmatory studies involve populations from study centers around the world, phase 2 studies (which precede confirmatory studies) are often based on relatively smaller numbers of patients from a limited number of centers in Europe, North America, or both regions. Hence, in phase 2 studies, variations in PRO data attributable to the influences of culture or region may not be pronounced. However, the sample-size calculations for the confirmatory studies, based on the variation found in phase 2 data, often neglect to include the possibility of added variation due to patients’ cultures and languages.

Variation in PRO data from MRCTs can be influenced by many factors including the availability and quality of cross-culturally validated PRO measures, the cultures represented among the study population, and the literacy level of the target patient population.

The ideal approach to cultural adaptation is to create PROMs with input from all the participating countries in the intended clinical trial; however, this is rarely done given the stringent timelines of drug development programs. As such, many PRO questionnaires are first developed in a single language (often US English) and then are translated into other languages to meet the needs of clinical trials. The translation of PROMs, also called cross-cultural adaptation, is a lengthy process to ensure linguistic, cultural, and psychometric equivalence among the various language versions [20].

Although the recognition for the need for culturally validated translation is not new, the application of methodological rigor employed in translating PROMs is recent [21]. Despite recent developments cultural equivalency of PROMs to be used in clinical trials cannot always be guaranteed for two main reasons.

Firstly, PROMs developed prior to the release of the PRO guidance by the FDA may not have employed appropriate methodology or the rigor that is required. During a recently reported translatability assessment of 13 PROMs culture contributed to the greatest discrepancy between the original and the target version [22].

Secondly, cultural equivalency may change over time. As with language, cultures are neither static nor discrete but an entity that constantly evolves and changes. What is considered to be acceptable at one point in time may not be so at a future time point [45]. For example, the Portuguese version of many PROMs had to be changed following the spelling reform introduced in 2012.

An important point to note is that emotions may be adequately translated but have different meanings and interpretations across cultures. For example, feelings such as frustration, shame, annoyance and anger may be expressed differently in different cultures leading to unexpected variation in reporting of symptoms as well as severity of symptoms [37]. For example, the mental health impact of irritable bowel syndrome, as measured by the SF-36,20 was shown to differ between patients in Greece and those in Sweden [23]. Reporting of symptoms associated with menopause varies among cultures [24], and in Asian cultures, depression is often expressed somatically (upset stomach, loss of appetite) rather than emotionally (feeling blue) [25]. In addition, varying attitudes among cultures toward diseases such as obesity [26] and AIDS [27] may also impact PRO data in MRCTs. For example fear of stigma and discrimination associated with HIV in parts of Africa prevents patients from reporting symptoms and seeking treatment [44].

Respondents’ literacy level, and thus their ability to read and comprehend instructions, questions, and response options and ability to utilize data capture technology, also may have an impact on the quality of PRO data in MRCTs. Researchers planning studies that include developing countries should note that literacy rates in some countries can vary significantly between urban and rural areas and between males and females. For example, the 2011 Indian census reports the literacy rate to be 80% in urban areas and 59% in rural areas [28]. Literacy rates can also vary significantly between males and females in some African and Middle Eastern countries [29].

Influence of geographical regions and culture is not unique to PRO data. Variation in health care outcomes due to factors such as socioeconomic status and cultural beliefs is frequently reported [30–32]. However, to maintain the integrity of a trial and to achieve the desired accuracy and reliability for an overall assessment of the effectiveness and safety of the study drug, it is important to consider the influence of language and culture on a PRO, especially if the PRO is the primary endpoint.

Knowledge of cultural nuances within the individual countries as well as literacy levels of the intended target population is essential for the successful outcome of a confirmatory clinical trial with PROs and to increase the generalizability of the PROMs. Such knowledge is best gathered through local, native-speaking health professionals who may provide an unbiased judgment of the proposed tools. On the basis of this knowledge, studies can be appropriately designed, PROMs improved (either through appropriate selection, modification or instruction) and the variability can be controlled, and the impact of these variations on the quality of
the study data can be minimized. Additionally, integration of new technologies, such as the use of IVRS may increase the ability for non-literate patients to participate in the collection of PRO data.

3.1.1. Potential for patient bias

Finally, an issue that is rarely discussed in PRO literature relates to the assumption that patients respond to questions relating to their feelings according to their own will, and without the influence of anyone else. Evidence to challenge this assumption is often found in literature relating to the ethical challenges in obtaining informed consent in biomedical research. In many group-oriented cultures it is often the opinion of the family or the community leaders that dictates an individual’s participation in clinical trials. Similarly in some cultures it is the power of the patient – based on factors such as socioeconomic background, caste, gender and age - in relation to the next of kin or the health care provider that determines his or her participation in clinical trials [33,34]. If a patient’s decision to take part in a clinical trial is not solely his or her decision then how much credibility can be placed on opinion about his or her feelings relating to treatment outcomes?

3.2. Complex study logistics

To include existing PROMs in MRCTs, comprehensive background information must be gathered. It is essential to select the appropriate version of the PRO measure to be used, obtain all necessary translations, receive permissions, if required, from authors and/or copyright holders; pay licensing fees [35] and verify the availability of certificates of translations to satisfy the needs of institutional review boards (in the US) and independent ethics committees (in Europe). Furthermore, it is important to ensure that an adequate supply of all necessary translations of the instruments in the appropriate data-collection formats (e.g., paper case report forms, digital devices) is available to patients when appropriate. Care must also be taken to determine if validation/equivalency data are available to support the mode of PROM administration or mix of modes of administration.

Many instruments have distinct versions for use in different situations, with varying recall periods or for subpopulations. For example, the AQLQ21 has an original version (published in 1991); a standardized version, both available as self- or interviewer-administered versions, and versions specific to children. Similarly, the SF-36 has version 1 (published in 1988) and version 2 (published in 1996). Both versions are available with a 1-month recall period (standard form) and a 1-week recall period (acute form).

Study teams should not underestimate the effort involved in obtaining all necessary translations required for multiregional studies. Many countries require more than one language. For example, if patients are to be recruited for a clinical trial in India, then PRO measures may have to be supplied in the 16 officially recognized languages in India. Even a small country like Switzerland requires PRO measures in three languages (German, French, and Italian) in local dialects.

Additionally, the linguistic similarity of a language spoken in different countries may differ significantly. For example, separate translations of French may be required for France, Belgium, and Canada; and separate translations for Tamil may be required for use in India, Sri Lanka, Malaysia, and Singapore.

Using the official languages of countries participating in MRCTs to guide the selection of languages for PRO measures may also be misleading. For example, although Latvian is the official language of Latvia, over a third of the population in Latvia speaks Russian only. Moreover, Swedish ethics committees often insist on patient access to a Danish version of PRO measures if study centers in Sweden are situated near the Danish border. In such cases, the integration of a Danish version of the relevant PROMs should be planned, even if no study centers in Denmark participate in the study.

The effort involved in ensuring the availability of the appropriate language versions for use in confirmatory clinical trials can be immense. Study teams must be aware of the location of the study centers and the composition of the expected patient population at these centers so that efforts can be targeted to the required language versions.

3.2.1. Study site training

Training of those who administer PROMs is critical for the collection of high quality data. Site staff must be prepared to provide clear instructions to participants on how and when to complete the study questionnaires to ensure the successful execution of a study. Administrators also should be fully trained to respond to queries and concerns from patients and/or caregivers as appropriate (e.g., if a patient is concerned about the confidentiality of his or her response on a PRO measure). Even if data suggests a treatment benefit, ambiguous instructions to patients for the completion of a PROM may result in regulatory concerns, such as in the review of a single item to assess itch for ustekinumab (STELARA: Janssen Biotech, Inc.: Horsham, Pennsylvania) [36].

3.3. Internal resource allocation

Inclusion of PROs in MRCTs can be time consuming and resource intensive for the sponsoring pharmaceutical company, requiring, among other activities, translations of questionnaires, organization of data-capture methods, preparation of training materials for study coordinators and patients, and compilation of briefing books to seek scientific advice. Inclusion of PROMs in study protocols also requires contribution from many functions internal to the sponsoring company such as clinical, data management, biostatistics, epidemiology, regulatory, communications, and outcomes research.

In the absence of an existing PROM fit for the required purpose, development of a novel PROM can be costly and take as long as 3 years; collaborative efforts may even take longer. A gap analysis early in a drug’s development is essential to assess the need for a new instrument and to initiate activities to ensure timely integration of the instrument in confirmatory clinical trials.

Considerable internal resources are required to integrate PROMs successfully into MRCTs. Often internal resources are secured when the intended PRO objective is specified as a “must have” in a strategic document such as the target market.
profile or target product profile [38]—that is, 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.

Whereas agreement would be clearly delineated when PRO is the primary endpoint, it may not be so when PRO is a nonprimary endpoint unless internal processes are in place to seek timely agreement. Lack of commitment from all parties often translates into poor implementation of PROMs in clinical trials leading to suboptimal data and missed opportunities.

3.4. Regulatory dilemmas

Companies face three options when PROs are expected to play a major role in regulatory decision making. First is the need to accommodate differing requirements and preferences by different health authorities to demonstrate treatment benefit, and the second relates to the path to developing PROMs required for a specific study. That is, the company has to choose between participation in a collaborative effort where the weight of validated evidence is likely to be great and regulatory feedback known or to follow a more traditional path (and shorter) of a single sponsor developing a novel PROM specific to a drug development program. A third option is to rely on an existing measure.

3.4.1. Differing requirements and preferences

The FDA and EMA appear to differ in their acceptance of PROMs in support of labeling claims. The FDA has demonstrated reluctance to provide label claims for PRO concepts other than symptoms whereas the EMA currently appears to take a more flexible approach approving label claims of higher order concepts such as HRQOL [3,36,39]. The EMA’s actions indicate greater openness to the inclusion of any scale providing it has been appropriately developed, has adequate psychometric properties, and its use can be justified for the study population [1].

Although there has been much emphasis on PROMs that are “fit for purpose” since the release of the FDA’s 2009 PRO guidance, a recent review of PRO labels from the FDA covering the period 2006–2010 showed that PRO label claims were granted “on the basis of measures that have been traditionally accepted by the reviewing divisions” [3].

Both FDA and EMA disease-specific guidelines frequently request PRO endpoints and even occasionally suggest specific questionnaires or PROs as primary or co-primary endpoints [39,40]. Moreover, although the FDA does not typically recommend HRQOL as a primary endpoint, the EMA recommends HRQOL as the primary endpoint in clinical trials for cystic fibrosis and as a co-primary endpoint in COPD and hematological malignancies [39].

Such differing requirements and preferences lead to an increase in the number of PROMs that must be included in a specific clinical trial. For example, in addition to demonstrating improvement in pain levels in RA [22] it is important to include both SF-36 and the HAQ-DI [23] to show functional improvement (FDA Guidance for Industry 2009) [6]. Furthermore, in RA studies the inclusion of a health-related quality of life measure is suggested by the EMA [41]. In addition, PROMs may be included to generate additional relevant information based on improvement in fatigue, work productivity, and health status—a total of five PROMs in addition to the measurement of joint pain.

Although differing requirements by differing regulatory agencies is not unique to PRO data [42], inclusion of multiple PROMs to satisfy the FDA and the EMA as well as payers may significantly increase the complexities associated with study logistics as well as the burden to patients who have to complete multiple questionnaires covering similar domains.

3.4.2. Collaborative, independent, or other approach

Multiple factors influence the decision of whether a pharmaceutical company will choose to invest with another in the qualification process for the development of a PRO, proceed with an independent development and validation process, or instead, rely upon existing measures that may or may not be appropriate for labeling claims. Importantly, this decision must be made very early in product development—often before the start of phase 2 studies when the target product profile is at early stages of development and when information may be too limited to allow a determination of the PRO concept to study. For example, the target population may not be specific enough, or the impact of treatment on the target population may not be certain until the end of phase 2 studies. Therefore, companies must decide between collaborating in the qualification process and choosing standalone development of a new PROM only if the tool will be utilized to define or support the primary endpoint or for disease areas in which a company is invested for the long term.

Alternatively, the determination to collaborate or “go it alone” may be determined by drug development timelines. Given the collaborative nature and the need for consensus building both within the working groups and with regulatory bodies, qualification of a PRO instrument may require 3 to 5 years. A home-grown measure, dependent upon the disease area, may typically have much shorter development times; however, the trade off is the weight of evidence and agreement amassed by the collaborative efforts compared to what is possible to achieve by a single entity.

3.4.3. Use of existing tools

A third option is not to participate in consortia or standalone development but rely on existing tools. Since some label claims from the FDA are still based on established and familiar PROMs, and the flexible approach shown by the EMA, companies pressed for development time and resources may still rely on traditionally used PROMs to generate value messages, especially for “well-researched diseases such as depression” where the regulatory path is well-established. However, this approach may not be suitable in the quest to provide patient relevant information, especially as the FDA PRO guidance continues to be integrated into the drug development process. Baldwin and colleagues [43] noted “...if regulatory hurdles to generate PRO based labeling claims hinder efforts to bring new medicines to the market in a timely manner, companies may invest in other innovative methods such as utilizing social media to communicate patient-based value messages to gain competitive advantage and address the needs of key stakeholders.

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22 Rheumatid arthritis.

23 Health Assessment Questionnaire—Disability Index.
outside the regulatory arena, such as payers, providers, and patients”.

4. Conclusion

The increase in the number of new therapeutic targets that affect global public health, changes in the regulatory environment, and business pressures resulting in increasing numbers of countries participating in clinical trials have had a significant impact on confirmatory clinical studies that incorporate PROMs in their assessments.

Recent changes within the regulatory environment in the US and Europe have challenged pharmaceutical companies to develop PRO strategies that satisfy health authorities globally. Regulatory guidance documents such as the FDA’s guidance for PROs and the FDA and EMA qualification processes have sought to simplify this process and increase transparency in the acceptance and use of these important PROMs. Collaborative efforts between regulatory bodies, the pharmaceutical industry, and PRO experts have further advanced the field of PRO research and the regulatory acceptability of PROMs. However, despite this progress, sponsors must tailor their regulatory strategy specific to the needs of each drug development program. The importance on the weight of “fit for purpose” evidence provided by the qualification process must be compared against competing priorities of drug development timelines, drug differentiation strategies, the need for patient-related value messages, and the depth of a sponsor pipeline within specific disease areas. These considerations often involve the needs of multiple stakeholders with competing priorities leaving study teams unable to formulate an effective PRO strategy. Regulatory acceptance of a wider number of PROMs in a larger number of disease areas may facilitate the development of future PRO strategies. Differences in regulatory needs between the FDA and EMA may always exist and teams will need to be poised to meet sometimes differing criteria.

Technological advances in data collection have enabled more control and may help ease some of the logistical complications in the execution of MRCTs in regard to data collection challenges. However, factors such as cultural relevance of concepts, literacy rates of respondents, cannot be controlled and must depend upon the quality of cross-cultural adaptation of PROMs and must continue to be part of the evaluative process when integrating PROs into confirmatory clinical trials. As a corollary to issues of cross cultural adaptation, we must be aware that some PRO data may be influenced by those other than the patient and may not be a reflection of the patient experience alone but instead a reflection of a more complex interaction between the patient, family, community or a physician/patient relationship. Teams must be aware of the needs and special challenges required and prepare for the resource needs to collect quality, evaluable PRO data so that the patient voice may continue to emerge from the context of confirmatory clinical trials. Awareness of the issues relating to PROs in multi-regional studies will enable companies to better plan studies, integrate PROs and interpret results.

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