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Systematic collection of patient reported outcome research data: A checklist for clinical research professionals

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ABSTRACT

Understanding the human experience is no longer an outcome explored strictly by social and behavioral researchers. Increasingly, biomedical researchers are also including patient reported outcomes (PROs) in their clinical research studies not only due to calls for increased patient engagement in research but also healthcare. Collecting PROs in clinical research studies offers a lens into the patient's unique perspective providing important information to industry sponsors and the FDA. Approximately 30% of trials include PROs as primary or secondary endpoints and a quarter of FDA new drug, device and biologic applications include PRO data to support labeling claims. In this paper PRO, represents any information obtained directly from the patient or their proxy, without interpretation by another individual to ascertain their health, evaluate symptoms or conditions and extends the reference of PRO, as defined by the FDA, to include other sources such as patient diaries.
Consumers and clinicians consistently report that PRO data are valued, and can aide when deciding between treatment options; therefore an integral part of clinical research. However, little guidance exists for clinical research professionals (CRPs) responsible for collecting PRO data on the best practices to ensure quality data collection so that an accurate assessment of the patient's view is collected. Therefore the purpose of this work was to develop and validate a checklist to guide quality collection of PRO data. The checklist synthesizes best practices from published literature and expert opinions addressing practical and methodological challenges CRPs often encounter when collecting PRO data in research settings.

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1. Introduction

Measurement of patient reported outcomes (PROs) offers researchers a unique lens into the patient's perspective and has been increasingly valued by both consumers and clinicians [1]. PRO data is provided directly by the patient without interpretation by another individual (e.g. clinician) in order to ascertain their health, evaluate symptoms or a condition and is based on the U. S. Food and Drug Administration's (FDA) definition of a PRO [2–4].When there are subtle differences between treatments, these data may provide the only evidence to suggest that one intervention is superior to another [5]. The inclusion of PRO measurement has been incorporated into the FDA's process for approval of new drug, biologic, and device applications [4,6]. The value of PROs is gaining momentum with changes to the Affordable Care Act prompting clinicians to elicit the patient's perspective, and may be linked to Medicare reimbursements in the future [7].

While social and behavioral researchers have historically included PROs as primary and secondary endpoints in their research, their inclusion are relatively new for many biomedical researchers. One review reported that approximately 30% (26,337 of 96,736) of biomedical trials included PROs as primary or secondary study endpoints [8]. Another review evaluating FDA new drug, device and biologic applications submitted between 2000 and 2012, found that 23% included PRO data to support labeling claims, and of those 81% included PROs as primary endpoints and 27% as secondary endpoints [9]. Formal integration of PROs into protocols with specific objectives demonstrates a researcher's commitment to quality PRO data collection [10] demonstrating that PROs are not merely “a fashionable add-on” but are imperative for clinical research [11] (p. 2). Despite increased use of PROs, less than 10% of protocols include specific instructions for the administration, collection and management of PRO measures and resultant data [12]. Research professionals who implement study procedures rely on the research protocol for guidance [13] which is often limited to the purpose and rationale for selecting a specific PRO measure [10, 14–16].

Based on the premise that the patient's perspective is a critical element of clinical research, the administration and management of these unique data should be rigorous to provide an accurate account

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of the patient's experience and avoid '*missing-ness*' [17]. Specific guidelines to improve reporting of PRO data have been published [2,18–22], and updates to U.S. and European regulatory guidance are continually reviewed and revised [23,24]. Non-profit organizations also provide expertise on PRO selection, implementation and methodological issues [25–27]. However, no single resource currently exists to guide quality data collection for clinical research professionals (CRPs) [28]. Therefore the purpose of this work was to apply an evidenced-based process to develop and validate a practical resource (checklist) for CRPs to guide the quality collection of PRO data, as compared to a per-protocol resource. For this work PRO is used as a term that broadly refers to any PRO measure, including questionnaires, instruments, diaries, or a survey (a collection of questionnaires) and focuses on pencil-and-paper measures.

2. Methods

2.1. Project initiation

Authors developed "how-to" instructions for CRPs that lacked experience with PRO data collection. In developing this informal resource it was realized that no comprehensive resource existed for CRPs. When reviewing the literature to validate the informal guidelines, the authors identified a gap in the published resources. It was determined that a comprehensive resource could have broader application and utility if developed. Although electronic collection of PRO data may resolve some of the methodological challenges CRPs encounter in paper PRO data collection, these systems are not universally used.

2.2. Literature review

A systematic literature search was conducted using the following electronic databases: CINAHL, Embase, Scopus and PubMed. Each database was searched individually and with varying combinations of the following list of terms: practical guidance, guideline(s), method(s), patient reported outcome(s), quality of life, health related quality of life, outcomes assessment, self-assessment, questionnaires, diaries, clinical trials, clinical research, clinical study(ies), and randomized controlled trial(s). The search was limited to articles published from 1990 to October 2015, English only and adult populations. An Internet search for practical guidance as well as descendency and ancestry approaches were used to find additional articles specific to this work (Fig. 1). Other gray literature was explored including unpublished work from within our organization and, as well as from professional nursing and research organizations to determine if formal guidance existed elsewhere.

2.3. Expert review

A draft checklist was developed, which combined evidence from the literature review with the initial informal resource. A group of experts were asked to review and provide feedback on the draft checklist. An 'expert' was defined based on their publication history and/or leadership experience in the use of PROs in clinical research settings. Five experts were identified and represented nursing and non-nursing, oncology and non-oncology clinical experts from a variety of roles such as research nurse study coordinator, scientist, and academic researcher. The checklist along with instructions and a reviewer feedback form were sent to each expert for an independent review. The workgroup collated the reviewers' feedback. All experts responded and a final checklist was developed after thoroughly considering all suggestions and achieving consensus by the authors.

3. Results

3.1. Expert reviewer feedback

Five experts provided feedback on the initial checklist. Reviewers rated the checklist using a 5-point scale, (1 = lowest and 5 = highest score) on the relevance, ease of use, literature support and overall quality. Overall scores ranged from 4.25–5 and individual items ranged from 4.6–4.8 (Table 1). A separate open-ended question asked reviewers if the guidance was clear and comprehensive. Each shared that the checklist was clear and that it provided a concise yet comprehensive list of all major points.

Reviewers also provided feedback for individual items. This included identification of specific areas that could use additional clarification and recommendations for newer literature to support items included; note that six additional articles were recommended by expert reviewers or were published after the literature search was initially conducted. Three reviewers recommended clarifying terminology (i.e. PRO vs. PRO instrument vs. PRO data) and adding additional qualifiers to some items such as assessing environment and influencing factors, adding the timing to complete PRO, and how to avoid bias. One reviewer also recommended including checkboxes for ease of use by CRPs. Two reviewers recommended including information about electronic-PRO as an administration mode. However the authors concluded that literature was unique and beyond the scope of this work.

3.2. Overview of checklist

The final evidence-based checklist (Fig. 2) represents a combination of the recommendations from the reviewed published literature, expert opinion, and the authors' experience to guide collection of PRO data by CRPs. The majority of articles reviewed were primarily expert guidance or individual center or researcher experience. Approximately 50% of the recommendations included in the checklist were not found in the literature but were conferred by experts or based on authors experience collecting PRO research data in clinical research settings.

The checklist is divided into two distinct sections: 'Pre-implementation' and 'Implementation', each representing different phases of a protocol's cycle. Pre-implementation includes front-end key considerations that occur during study development, such as design, data management, formatting and staff training. Though it is generally understood that the CRP may have limited input into the development of the study design, this information was included in the checklist to offer a comprehensive resource for CRP staff overseeing the administration of PRO data collection. The 'Implementation' section covers the period just prior to when the CRP administers the PRO survey, through administration, and post-administration; primarily focusing on guidance for PRO collection from the study participant. This part of the checklist includes specific actions for the CRPs involved in PRO data collection.

3.3. Pre-implementation

The majority of the work in this area has focused on study development and design. There are numerous sources that support the considerations in the front-end development of a research study that includes PRO data collection. While CRPs may not be routinely involved in the study design phase of protocol development, their expertise with a specific population, disease or setting may be valuable in recognizing factors that ultimately influence the study design and completion.

3.3.1. Study development & design

3.3.1.1. Standardizing data collection procedures. When developing a study, standardizing data collection practices is strongly recommended [29]. Multiple articles made recommendations to standardize data collection practices such as: mode(s) of administration (self-reported vs.