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DOI:
10.1038/s41591-021-01648-4

The Value of Patient-Reported Outcomes in Early Phase Clinical Trials

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If used correctly, patient-reported outcomes can provide preliminary evidence of efficacy and tolerability from a patient perspective, as well as supporting regulatory review.

Early phase clinical trials are essential to drug development, enabling insight into how new drugs interact with the human body, their safety profile and side-effects associated with dosage adjustments [1]. Traditionally, drug activity and safety have been monitored and documented using investigator-assessed clinical tools. However, these trials offer a unique opportunity to gather preliminary evidence on the benefits and risks of therapeutics from the patient perspective [1].

Why PROs matter

Patient-reported outcomes (PROs) could play an important role in early phase trials by facilitating the assessment of preliminary efficacy and tolerability, and using patient experience to inform dose selection for later phase trials through symptomatic identification of toxicities. Additionally, PRO feasibility data gathered during early phase trials can enhance future PRO strategy in later phase studies, promoting efficient use of measures; and data completeness, as well as informing future analyses and sample size estimation. Use of PROs in an early phase setting also facilitates identification of challenges to PRO completion such as availability of

patient materials in appropriate languages, acceptability of PRO assessment to participants, and availability of appropriate modes of PRO delivery.

Qualitative data collection alongside the early phase trials can provide further insight into participant experience of providing PRO data, highlighting the barriers and facilitators. This ensures the PRO data are relevant to patients, practical considerations are assessed, and issues of inclusion and diversity can be explored. These steps increase the potential generalisability of findings by enhancing participation at later trial phases and may improve data quality for regulatory review (Figure 1).

Inclusion of PROs in early phase trials is gradually increasing [2, 3] with examples in oncology and inflammatory disease though use inPhase I patient trials remains low [4].

Developing a PRO strategy

A number of methodological considerations should be addressed when developing a PRO strategy for early phase trials. These include selecting concepts of interest through early engagement with regulators, trial management groups, and patient partners; and developing a PRO research question through identification of key outcomes, rationale for assessment and those that can be assessed using PRO measures through qualitative research with patient groups, literature review and core outcome sets[5]. PRO efficacy and AE measures are selected following assessment of psychometric properties to ensure their use is appropriate in the target population and that they measure concepts that are clinically relevant and important to patients. Measures for patient self-reporting of symptomatic AEs are selected through review of safety profile data and availability of patient-reported AE tools. Gaps in existing

tools can be identified through engagement with the trial management group and patient partners, and may be addressed by developing new items with the instrument licence-holders. A key challenge of early phase studies is the limited availability of safety profile information, so determining which outcomes to assess *a priori* may prove difficult. A case by case approach will allow for identification of these data where available. The schedule of assessment may differ for efficacy and tolerability outcomes depending upon the anticipated pattern of responses to the treatment being studied. PRO endpoints should be specified in advance, including for descriptive or exploratory analyses[6] (Figure 2).

Patient-Reported Adverse Events (AEs) and Tolerability

Traditional measures to assess safety and tolerability, such as the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), rely on clinical report[7]. However, symptomatic adverse events can be under-reporteded by clinicians[8]. To address this, patient-reported AEs, toxicity and tolerability reporting could also be used early in the drug development pipeline.

For example, PRO-CTCAE was developed to characterise these from the patient perspective, to generate information that complements CTCAE data and provide a holistic insight into patient experience of treatment, which is integral for clinical decision-making. Together, the CTCAE and PRO-CTCAE can inform more patient-relevant dose selection[9], identification of symptomatic toxicities[10] and the planning of toxicity management.

In oncology, the PRO-CTCAE has demonstrated favourable psychometric properties[11] though its use outside of oncology is novel. Wide use of the CTCAE and the comprehensive nature of the PRO-CTCAE mean its potential for use in other conditions may be substantial. Further research to validate the PRO-CTCAE and assess its acceptability outside oncology are therefore required.

In an oncology setting it has been suggested that a sub-set of the 124 PRO-CTCAE items can be used to minimise patient burden, and where limited drug activity and safety profile data is available, selection may be based upon focused evidence identification[12]. Potential sources of evidence include non-clinical data, other early phase studies; multi-disease trials using the same compound; AEs from pre-existing treatments for the disease; AEs of interest to patient groups in question; AEs identified by other multi-stakeholder groups; those observed in animal studies. However, scarcity of available data; AE under-reporting; use of different adjunct therapies (including treatment combinations) across trials; and in the case of basket trials, interaction between underlying disease and physiology resulting in a different disease profile and a range of potential AEs presents significant challenge to this approach.

In such instances and for use outside of oncology, the entire item library such as the PRO-CTCAE may be presented with a free text box for unanticipated symptoms. Delivered electronically to minimise patient burden[13], this avoids potential channeling of patients to pre-selected items. Use of global tolerability items such as the Functional Assessment of Cancer Therapy – General (FACT-G) single item GP5 (“I am bothered by side effects of treatment”) can also provide valuable data in early phase trials [14].

Patient-reported AEs may use different schedules of events compared to the PROs linked with efficacy outcomes, for example they may be more frequent following initial treatment administration[15].

Regulatory Considerations

Used appropriately, PRO data can support regulatory decision making by providing the patient perspective. The US Food and Drug Administration (FDA)'s Patient-Focused Drug Development meetings demonstrate growing interest in patients' understanding of therapies [16]. This is in addition to their existing guidance [17] applicable to a confirmatory study context.

The UK's Medicines and Healthcare products Regulatory Agency (MHRA) are increasingly interested in PRO data [18]. Its Innovative Licensing and Access Pathway (ILAP) [19] has a specific focus on patient engagement and includes multi-agency discussions around PRO inclusion in the clinical trial programme which may help sponsors consider strategic PRO objectives.

PROs can be included in early phase studies if they support future development [20], and regulators use PRO data from confirmatory studies in their decision-making processes. However, there is a growing interest in using PROs to inform on patient tolerability [21]. With more rigorous patient-reported instruments available, these data could supplement traditional approaches to determining the recommended dosing. Early regulatory engagement through scientific advice ensures alignment on trial design, instrument selection, analysis and interpretation [22].

Innovative Trial Designs

Novel trial designs may make the PRO selection more challenging. In basket trials, for example, patients are assigned to trial arms according to molecular drivers rather than their specific diagnosis [23]. In this context, the PRO strategy should maximise comparability between arms while still covering aspects important to specific patient cohorts and key stakeholders.

Early phase trials are signal seeking and use small sample sizes so they require a sensitive PRO strategy that complements the other forms of data collection. As well as providing preliminary evidence of therapeutic responses and tolerability, PRO assessment in early phase trials can inform future sample size strategies and identify which trial arms should proceed for further study. Input from patient partners through actively managed involvement processes is required throughout. The extent that PRO data can inform benefit risk assessment in a single early phase trial is limited where randomisation or controls are not used. However, PRO use yields valuable insight, enhancing the evidence base, and informs methodology development.

[Figure legend Figure 1: The benefits of including patient reported outcomes in early phase trials]

[Figure legend Figure 2: Considerations for developing a patient reported outcome assessment strategy in early phase clinical trials]

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Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by the National Institute for Health Research (NIHR) Birmingham Biomedical Research Centre, Midlands-Wales Advanced Therapies Treatment Centre (MW-ATTC) programme grant from Innovate UK to a consortium of partners including Health Technology Wales, the Welsh Blood Service and the University of Birmingham (Grant number: IUK: 104232) and Innovate UK (part of UK Research and Innovation) grant Patient-reported outcomes assessment to support accelerated access to advanced cell and gene therapies: PROmics (Grant No: 104777). The funder was not involved in any aspect of the research work. OLA/AR and MC receive funding from the NIHR Applied Research Collaboration, West Midlands (ARC) and the Brain Tumour Charity. OLA receives funding from the NIHR Birmingham Biomedical Research Centre (BRC, West Midlands at the University of Birmingham and University Hospitals Birmingham NHS Foundation, Innovate UK (part of UK Research and Innovation), Gilead Sciences Ltd, and Janssen Pharmaceuticals, Inc.

MC is Director of the Birmingham Health Partners Centre for Regulatory Science and Innovation, Director of the Centre for Patient Reported Outcomes Research and is a National Institute for Health Research (NIHR) Senior Investigator. She receives funding from the NIHR, UK Research and Innovation (UKRI), NIHR Birmingham Biomedical Research Centre, the NIHR Surgical Reconstruction and Microbiology Research Centre and UK SPINEat the University of Birmingham and University Hospitals Birmingham NHS Foundation Trust, Health Data Research UK, Innovate UK (part of UKRI),Macmillan Cancer Support, UCB, Gilead, Janssenand GSK Pharma.

The views expressed in this article are those of the author(s) and not necessarily those of the NIHR, or the Department of Health and Social Care or the MHRA.

Competing interest

OLA declares personal fees from Gilead Sciences Ltd, GlaxoSmithKline (GSK) and Merck outside the submitted work.

MC has received personal fees from Astellas, Aparito Ltd, CIS Oncology, Takeda, Merck, Daiichi Sankyo, Glaukos, GSK and the Patient-Centered Outcomes Research Institute (PCORI) outside the submitted work.

Other authors declare no competing interests.

Acknowledgments

We thank Drs Andrew Filer, Palak Trivedi, Dimitrios Chanouzas, and Profs Subrata Ghosh and Amylou Dueck for their advice and suggestions during this project.