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Patient-reported outcome measures add value as clinical trial endpoints

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Asking patients about their symptoms, functioning, and well-being during clinical trials can influence trial outcomes, regulatory decisions and clinical practice.

Randomized clinical trials (RCTs) are the gold-standard for assessing novel interventions in health. Traditionally, RCTs have used endpoints derived from physiologic and laboratory measures, clinician-reported outcomes, and performance outcomes to assess the effect of interventions. More recently, patient-reported outcomes (PROs), which are collected directly from patients to describe how they feel, function, and live their lives, are being included as endpoints in RCTs to better understand the effect of the intervention from the patient perspective. PRO measures are validated, standardized questionnaires to assess diverse outcomes such as health-related quality of life (HRQoL), physical functioning, emotional/mental wellbeing, symptoms, and cognitive function. PROs can be included in RCTs as primary, secondary, or exploratory outcomes, and as a stand-alone or part of a composite outcome.

In this comment, we highlight instances where PRO endpoints in clinical trials have provided valuable insight into the benefits and burdens of interventions beyond that collected by physiologic, laboratory, clinician-reported, observer-reported, or performance outcomes alone (see Box). We do this by highlighting examples of trials conducted across clinical specialties where findings from PRO data had demonstrable impact on decision making in clinical, regulatory, and health policy contexts.

PROs as primary endpoints

PROs are increasingly serving as the primary endpoints of RCTs. In these instances, PRO data are, by definition, pivotal in decision making. For example, in the ADAPT trial to evaluate efgartigimod for generalized myasthenia gravis, the PRO Myasthenia Gravis Activities of Daily Living (MG-ADL) score was used as the primary endpoint. Responders were defined as those experiencing a 2 point or greater improvement in the MG-ADL score for at least 4 consecutive

weeks.¹ Efgartigimod ultimately showed a clinically and statistically significant benefit versus placebo during the first treatment cycle (68% vs 30% respectively). The ADAPT trial was cited in the FDA label and press release as the basis for drug approval. Findings from this study have also informed practice guidelines as well as cost-effectiveness analysis.

A PRO was also the primary endpoint in the MUSCA trial, which evaluated mepolizumab add-on therapy for patients aged 12 years and older with severe eosinophilic asthma.² The primary outcome was the total score from the St. George's Respiratory Questionnaire (SGRQ), a respiratory-specific HRQoL measure that assesses symptoms, activities and impact. Mepolizumab demonstrated a benefit in total SGRQ score compared to placebo as determined by mean change score from baseline (15.6-point improvement for mepolizumab vs. 7.9 for placebo). Findings from the MUSCA trial were included in the FDA label for mepolizumab, providing insights regarding the impact of experiencing multiple exacerbations beyond a simple count of days with exacerbation events. This was the first time a label for an asthma treatment included the SGRQ, which had been more widely used in chronic obstructive pulmonary disease. Beyond inclusion in the product label, this trial has been cited in clinical guidelines and was a factor in mepolizumab receiving a 'conditional recommendation' from the European Academy of Allergy and Clinical Immunology for asthma sufferers.

Surgical studies have also included PROs as primary outcomes. The SAMS trial evaluated a combined palatal and tongue surgery for patients with obstructive sleep apnea who are unable to use devices.³ The patient-reported Epworth Sleepiness Scale was the co-primary outcome of the SAMS study, alongside the apnea-hypopnea index. Combined surgery showed a benefit in both outcomes compared to the medical management group. In addition, the magnitude of improvement was larger for patient-reported sleepiness than for apnea events per night.⁴ Findings from the SAMS trial have been included in consensus and position statements related to the role of surgery in obstructive sleep apnea, where PRO findings from this trial are

used to highlight the potential benefit of surgical approaches for a condition otherwise managed through medical devices.

A fourth study illustrates the value of PROs as a primary endpoint for the common condition of adult lumbar spondylolisthesis causing lower back pain. The study randomized patients to Spinal Laminectomy vs. Instrumented Pedicle Screw spinal fusion (the “SLIP” trial) to test the hypothesis that, compared to laminectomy alone, laminectomy with fusion would result in greater improvement in the physical component summary (PCS) score of the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36) at two years.⁵ Results showed clinically significantly greater improvement in SF-36 PCS scores in the laminectomy with fusion group (improvement of 15.2 vs. 9.5 points), which remained statically significant at three and four years. This trial was an important component of a meta-analysis that confirmed superior outcomes with fusion surgery across trials in this condition and informed practice guidelines accordingly.

PRO as part of a primary, composite endpoint

As part of composite endpoints, PROs integrate the patient perspective with other measures of clinical relevance. The TRILUMINATE trial was an RCT comparing tricuspid transcatheter edge-to-edge repair (TEER) to medical therapy in severe tricuspid regurgitation.⁶ The primary composite endpoint included death; hospitalization for heart failure; and an improvement in HRQoL measured using the Kansas City Cardiomyopathy Questionnaire (KCCQ) at 1-year. While the incidence of death and rate of hospitalization for heart failure did not differ significantly between groups, patients in the TEER group were almost twice as likely to report a clinically meaningful improvement in HRQoL and functional outcomes on the KCCQ. The TRILUMINATE trial is cited in clinical practice guidelines. It also heavily

informed health technology assessment review conclusions that TEER may be more effective at improving HRQoL than medical therapy alone.

A second example where a PRO was used as part of a primary composite endpoint was in the study of tocilizumab for the treatment of juvenile idiopathic arthritis.⁷ In this study of children aged 2-17 years, the primary outcome was an absence of fever and percent of participants improving by at least 30% on three of the six variables in the American College of Rheumatology core set for juvenile idiopathic arthritis [JIA ACR 30]. The core set includes i) number of joints with active arthritis, ii) number of joints with limited range of motion, iii) physician's global assessment of disease activity, iv) parent or patient's global assessment of well-being, v) physical function assessed using the Disability Index of Childhood Health Assessment Questionnaire, and vi) erythrocyte sedimentation rate. More patients in the tocilizumab group achieved improvement on the composite endpoint compared to placebo (85% vs. 24%). In addition to being part of the primary outcome, PRO measures collected in the open-label extension of the study demonstrated clinically relevant improvement in physical function. Benefits in JIA ACR 30 and clinical outcomes were cited as the basis for regulatory approvals of tocilizumab, were used to inform clinical practice guidelines, and informed cost-effectiveness analyses.

PROs as secondary endpoints

As secondary endpoints in clinical trials, PROs can support the primary outcome regarding the value of a treatment or intervention, or contradict the primary outcome findings, providing contrasting information.

The CABANA trial was an RCT of catheter ablation versus antiarrhythmic drug therapy among patients with atrial fibrillation (AF).^{8,9} This trial demonstrates how important secondary PRO results provide context for clinical care when there is a null finding for the primary

outcome. The primary outcome was a composite endpoint of death, disabling stroke, serious bleeding, and cardiac arrest. Secondary outcomes included the Atrial Fibrillation Effect on Quality of Life (AFEQT) summary score and the Mayo AF-Specific Symptom Inventory (MAFSI). The primary outcome showed no significant difference in the intention-to-treat population, with a wide 95% CI around the effect estimate. However, the PRO secondary outcomes demonstrated significant and clinically important benefits of the ablation strategy, both in terms of total disability scores (AFEQT) and overall symptom scores (MAFSI). The CABANA trial was acknowledged in the 2020 European Society of Cardiology guidelines for the diagnosis and management of atrial fibrillation, where it was specifically cited as evidence that catheter ablation can reduce arrhythmia-related symptoms, supporting the role of ablation for this indication. Additionally, HRQoL data are the primary basis for ablation meeting criteria for economic attractiveness relative to drug therapy.

The ISCHEMIA study was an RCT comparing an initial invasive strategy (angiography and revascularization) versus conservative medication therapy alone in patients with myocardial ischemia.^{10,11} The primary outcome was a composite of death from cardiovascular disease, myocardial infarction or hospitalization for unstable angina, heart failure, or resuscitated cardiac arrest. Health status measured by the Seattle Angina Questionnaire was a secondary outcome, and included angina-related symptoms, function, and HRQoL. While the trial showed no survival benefit in the use of an invasive strategy, those who received the invasive therapy reported substantial improvement in angina symptom severity scores versus medical therapy alone. The PRO data were recognized in clinical practice guidelines as evidence of the importance of informing patients about the risks and benefits of an invasive versus more conservative approach to manage stable ischemic heart disease.

The third example of an RCT where the PRO secondary outcome had a meaningful impact is a study of recombinant human erythropoietin (rHuEPO) for the treatment of anemia in

pre-dialysis patients.¹² The primary study outcome was amelioration of anemia, which was observed for those receiving the rHuEPO intervention. HRQoL was evaluated as a secondary outcome using three 10-point linear visual analog scale questions assessing energy level, ability to do work, and overall HRQoL. Findings from the HRQoL data supported the primary endpoint, with HRQoL improving for those in the rHuEPO group compared to those in the control group. This study was one of six studies included in a Cochrane review which collectively informed UK National Institute for Health and Care Excellence guidelines indicating that HRQoL should be considered when making decisions about use of rHuEPO in pre-dialysis patients.

CONCLUSION

PRO findings from RCTs, as either primary or secondary measures that were either stand-alone or part of a composite endpoint, have influenced clinical decision making and health policy across diverse medical specialties (see Figure). Illustrative trials presented here demonstrate the growing value of PROs in clinical research, and the clear and transformative impact that PRO findings can have on medical practice (see Box). These trials demonstrate that collecting outcome data via direct patient report can provide insights which could not have been ascertained through physiologic, laboratory, clinician-reported, observer-reported, or performance outcomes alone.

PROs in RCTs provide valuable information across diverse medical specialties, conditions, and healthcare interventions. By demonstrating the value-added by PRO endpoints in these RCTs, we aim to encourage the widespread and rigorous inclusion of relevant PRO endpoints to optimize their impact on clinical practice and health policy. The value of PROs in RCTs can only be realized if PRO methods are appropriately designed and rigorously executed. Guidance is available to support developing protocols that include PROs, selecting appropriate PRO measures, analyzing data, reporting and visualizing results, and applying findings in

practice. Groups such as the [PROTEUS Consortium](#) (Patient-Reported Outcomes Tools: Engaging Users and Stakeholders) curate established resources to optimize the use of PROs in clinical trials, as well as in clinical practice.¹³ Perhaps unsurprisingly, the trials included in this paper were found by our authorship team to be well designed and reported.

Collecting data directly from patients broadens our understanding of novel health interventions, providing insights which could not have been ascertained by other types of measures. By demonstrating the value added by PRO endpoints, we aim to promote their rigorous integration into RCTs, thereby enhancing the benefit to clinical practice and health policy.

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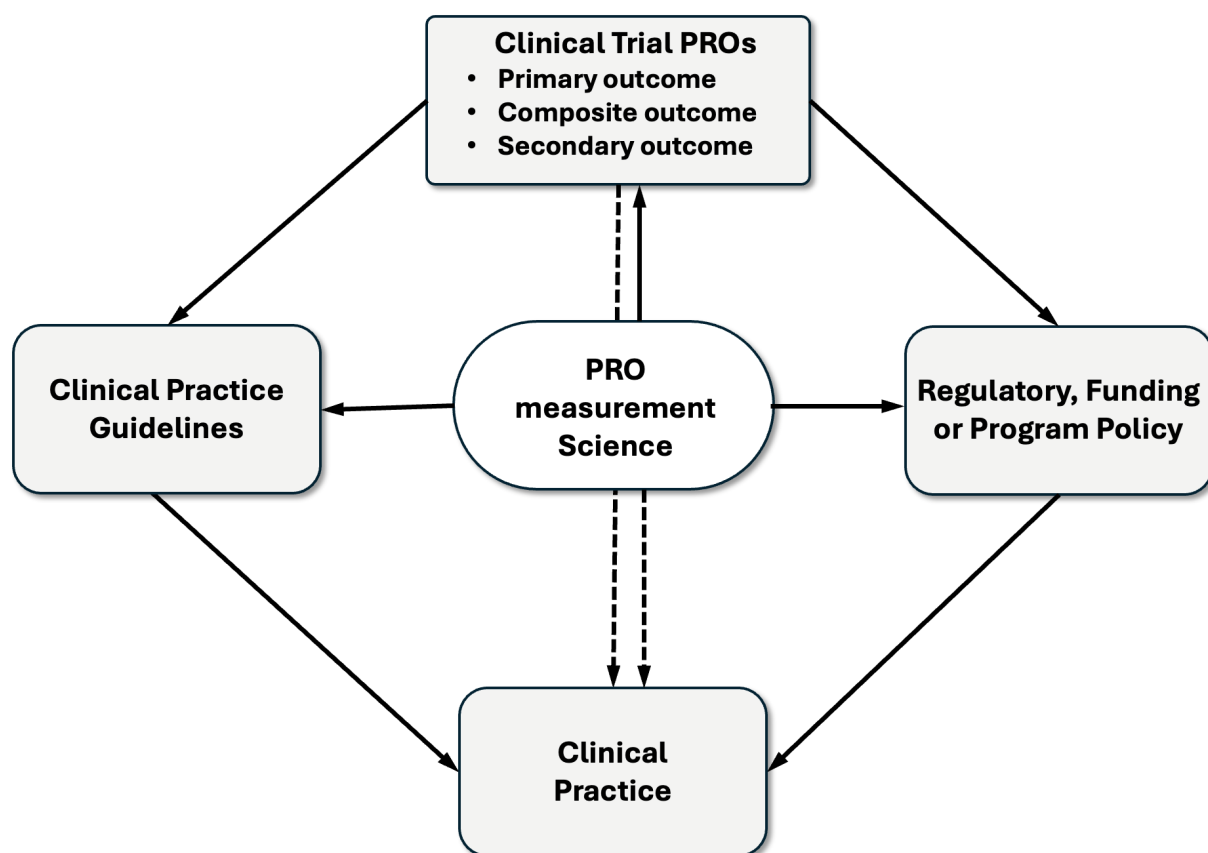
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Competing interests:

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Figure: Use of PROs in clinical trials impacts medical practice and policy



Footnote: Dotted lines are weaker relationships, solid lines are stronger relationships

Box: Role and value of PROs as clinical trial endpoints

PROs as primary endpoints

- PRO data is the primary evaluation of the intervention
- Information collected from the patient's perspective is inherently integrated into decisions made based on the trial's findings
- *Example:* In the ADAPT trial¹ of efgartigimod for generalized myasthenia gravis, the disease-specific PRO measure MG-ADL demonstrated clinically and statistically significant benefit of the treatment vs. placebo, and was cited as the basis for FDA approval, included in the product label, and informed practice guidelines and cost-effectiveness determinations.

PROs included as a part of a composite primary endpoint

- PRO data, in combination with other outcomes, is used to evaluate the intervention
- Information collected from the patient's perspective, combined with data collected from other perspectives, is used to evaluate the intervention
- *Example:* De Benedetti et al. trial⁷ of tocilizumab for juvenile idiopathic arthritis used the JIA ACR 30 composite endpoint, which includes patient (or parent) reported data on global well-being and physical function. More patients in the tocilizumab group achieved improvement on the composite endpoint, which informed drug approvals, clinical guidelines, and cost effectiveness.

PROs as secondary endpoint

- PRO data demonstrates the intervention's benefit or burden beyond conventional endpoints
- Information collected from the patient's perspective complements the primary evaluation of the intervention, either supporting, contrasting, or providing additional insight into the intervention's impact
- *Example:* CABANA trial^{8,9} of catheter ablation vs. antiarrhythmic drug therapy for atrial fibrillation had a null finding for the primary outcome, but secondary PRO results demonstrated significant and clinically important benefits of the ablation strategy, both in terms of total disability scores and overall symptom scores. These results helped provide context for clinical care and informed management guidelines and economic analysis.

Abbreviations: PRO (patient-reported outcomes); MG-ADL (Myasthenia Gravis Activities of Daily Living); JIA ACR 30 (American College of Rheumatology core set for juvenile idiopathic arthritis)

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