The Impact of Patient-Reported Outcomes in Market Access: A Literature Review, Regulatory Evidence Assessment Framework and Study

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Aim

A literature review was conducted to identify research related to patient-reported outcome (PRO) impact on regulatory, health technology assessment (HTA) and market access (MA) milestones. From this, a framework was then developed and validated to assess the impact of PRO evidence on regulatory approvals.

Introduction

- PROs are self-reported health outcome measurements that come directly from the patient without amendment or interpretation by a clinician. They focus on the patient experience beyond strictly clinical outcomes. Despite 2009 FDA guidelines[1] on PRO use, it is unclear how PRO evidence influences drug approval and patient access.[2]
- EQ-5D is often used to capture health-related quality of life (HRQoL) in adults; however, previous studies have indicated its lack of responsiveness in certain conditions.[3] Questionnaires that explore relevant, disease-specific domains are more highly regarded by regulatory agencies.[2] The impact of non-EQ-5D PRO evidence in supporting drug approval and access was investigated across three key milestones:
  - **Regulatory milestone**: drug approval and labelling by regulatory agencies (FDA and EMA)
  - **HTA milestone**: drug pricing and reimbursement by HTA agencies (NICE and SMC)
  - **MA milestone**: patient access to drugs, uptake and implementation in clinical practice.

Literature review: methods

- A literature review was performed to identify research exploring the impact of PROs across the three milestones. Searches were conducted in Embase, Medline, Medline In-Process and other non-indexed citations, and the REF 2014 Impact Case Studies database[4] from 1 January 2009 to 18 August 2020 to coincide with the publication of FDA guidelines.[1]
- The search identified any PRO studies reporting on HRQoL, symptoms and/or functioning in a regulatory, HTA or MA setting. The search excluded EQ-5D, patient preference studies (due to restriction of patient's choice), proxy-reported outcomes and clinician-assessed outcomes.

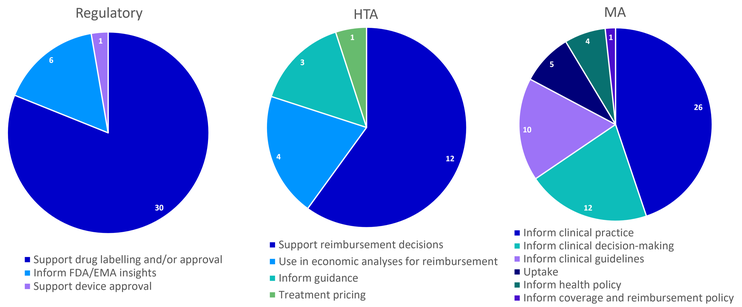
Literature review: results

- The literature review identified 77 studies, some covering more than one milestone. PRO impact categories are summarised in Figure 1.
- **Regulatory milestone (37 studies):**
  - PROs were mainly considered as supporting evidence for drug approvals, indications and/or label claims (30/37 studies).
  - Historically, patient perspectives are underrepresented in clinical trials[4] used for regulatory purposes and are rarely included in drug labelling.[5] The EMA was more likely to grant PRO claims, which suggests differences in evidentiary standards have existed.[6]
- **HTA milestone (19 studies):**
  - PRO evidence is important in informing economic analyses;[7] however, the lack of guidance by HTA agencies on conduct and reporting of PRO data affects the overall inclusion of quality PRO evidence in HTA submissions.
- **MA milestone (47 studies):**
  - Clinicians recognised the benefit of PROs in clinical practice on improving processes of care, communication, and joint decision-making;[9] however, clinicians were found to be reluctant to collect PRO data due to perceived workload and uncertainty in their interpretation of results.[10-12]
  - There was substantial heterogeneity in the methods and metrics used to report PRO impact in MA making results difficult to synthesise.

Framework and study: methods

- A framework was developed to assess PRO impact on the regulatory milestone.
- For each approval, the FDA Drug Approval Package (DAP) and Prescribing Information (PI) documents or the EMA European Public Assessment Reports (EPAR) and Summary of Product Characteristics (SmPC) were searched.
- PRO impact was categorised as "substantial" if PRO evidence was included in the drug label or it could be inferred this evidence directly impacted recommendations.
- This framework was validated in a study of 20 regulatory approvals (10 EMA; 10 FDA) which used PRO data, published 28 August 2018–6 November 2020 across a range of therapy areas.

Figure 1. PRO impact categories across the three milestones



Framework and study: results

- All submissions reported PRO evidence as a secondary or exploratory trial endpoint.
- A range of disease areas were explored with oncology (9/20) and neurology (6/20) selected most frequently.
- PRO evidence was supplemented by patient diaries in two drug submissions (fremanezumab (*4833 [EMA]; FDA 761089 [FDA]*) and selpercatinib (*213246 [FDA]*).
- All but one submission included disease-specific questionnaires, whilst general questionnaires were used in 9/20 submissions.
- In three approvals, PROs were deemed to have "substantial" impact as the inclusion of PRO evidence appeared to directly impact approval and PRO claims were granted.
  - *5269 (EMA)*: Ivacaftor/Tezacaftor/Elexacaftor received a disease-specific questionnaire claim (Cystic Fibrosis Questionnaire-Revised [CFQ-R]).
  - *4833 (EMA)/ 761089 (FDA)*: The fremanezumab appraisal used data from patient diaries, which included a statistically significant reduction of monthly headache hours used to inform the primary outcome. The EMA also granted claims for two migraine specific questionnaires (MIDAS, HIT-6).
- The remaining 17 approvals were not considered to have substantial impact. Six were critiqued by the regulatory body (quality of PRO data, trial design, insufficient data, content validity issue with PRO measures, and applicant didn't propose any labelling claims), and PRO evidence was found to be either: not statistically significant or not analysed; had a disagreement on threshold for clinical significance; or PROs were not fully reported in the remaining 11 approvals.

Figure 2. Barriers to PRO impact identified in the literature review

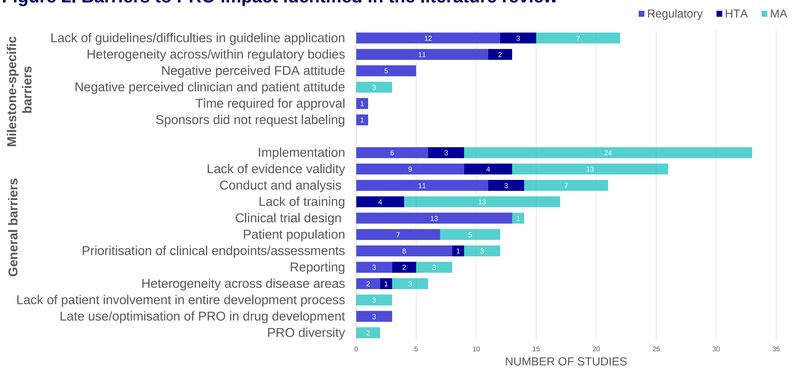
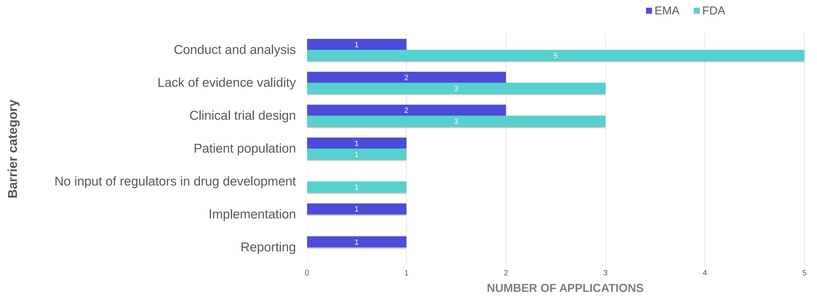


Figure 3. Barriers to PRO impact in regulatory approvals



Barriers to PRO impact

- Barriers to PRO impact were reported across the literature review (Figure 2) and study (Figure 3).
- Literature review barriers were assessed as general or milestone-specific. The most frequently reported milestone-specific barrier across all three milestones was lack of guidelines and/or difficulty in guideline application. The most frequently reported general barriers were: "implementation", "lack of evidence validity" and "conduct and analysis".
- The main barriers identified in the study are comparable to those identified in the literature review: conduct and analysis (6/20); lack of evidence validity (5/20); and clinical trial design (5/20).

Study limitations

- The regulatory study could only consider information in the public domain, and only used a small study sample so findings may not be generalisable.
- It is challenging to assess the extent to which the PRO evidence had an impact on regulatory decisions as it is not often clear whether a PRO claim was made or the reason for a claim to be granted or denied.
- The retrospective nature of this study does not capture the ongoing development and progress being made by regulatory agencies. The EMA is currently aiming to revise existing patient engagement methodology and guidelines to encourage and facilitate greater patient involvement throughout the regulatory process.[13, 14] The FDA also has an extensive Patient Focused Drug Development (PFDD Programme).[15]

Conclusions and implications

- There is a large body of research exploring the role of PROs in drug development decision-making, particularly to determine PRO impact on drug labelling and approval.
- As seen in the framework synthesis and study, PRO data claims can have a substantial impact on approval. However, challenges to the applicability of the selected PRO, and to their conduct and analysis often prevent a positive claim. There is an opportunity for manufacturers and regulatory authorities to collaborate in development so that PRO data is fit for the intended purpose and could be used in both regulatory and reimbursement applications globally.
- Currently, many PRO tools are not adequately robust to inform regulatory benefit-risk decisions. Further development of disease-specific or appropriately sensitive tools is required.[16]
- It is difficult to assess the impact of PRO evidence on regulatory approval. We encourage regulators to be more transparent in the assessment of PRO evidence in EPARs and label claims. This could be achieved by publishing a summary of patient experiences/input provided during development and in the final submission along with its interpretation and analysis.[2]

Abbreviations (not defined in text): EMA, European Medicines Authority; FDA, Food and Drug Administration; NICE, National Institute for Health and Care Excellence; SMC, Scottish Medicines Consortium

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