

UNIVERSITY OF BIRMINGHAM

University of Birmingham
Research at Birmingham

Harnessing the patient voice in real-world evidence

Calvert, Melanie; O'Connor, Daniel J; Basch, Ethan

DOI:

[10.1038/d41573-019-00088-7](https://doi.org/10.1038/d41573-019-00088-7)

License:

Other (please specify with Rights Statement)

Document Version

Peer reviewed version

Citation for published version (Harvard):

Calvert, M, O'Connor, DJ & Basch, E 2019, 'Harnessing the patient voice in real-world evidence: the essential role of patient-reported outcomes', *Nature reviews. Drug discovery*. <https://doi.org/10.1038/d41573-019-00088-7>

[Link to publication on Research at Birmingham portal](#)

Publisher Rights Statement:

Checked for eligibility: 04/07/2019

This document is the Author Accepted Manuscript version of a published work which appeared in its final form in Nature Reviews Drug Discovery. The final version of record can be found at: <https://doi.org/10.1038/d41573-019-00088-7>

This work is subject to Springer Nature re-use terms: <https://www.nature.com/nature-research/editorial-policies/self-archiving-and-license-to-publish#terms-for-use>

General rights

Unless a licence is specified above, all rights (including copyright and moral rights) in this document are retained by the authors and/or the copyright holders. The express permission of the copyright holder must be obtained for any use of this material other than for purposes permitted by law.

- Users may freely distribute the URL that is used to identify this publication.
- Users may download and/or print one copy of the publication from the University of Birmingham research portal for the purpose of private study or non-commercial research.
- User may use extracts from the document in line with the concept of 'fair dealing' under the Copyright, Designs and Patents Act 1988 (?)
- Users may not further distribute the material nor use it for the purposes of commercial gain.

Where a licence is displayed above, please note the terms and conditions of the licence govern your use of this document.

When citing, please reference the published version.

Take down policy

While the University of Birmingham exercises care and attention in making items available there are rare occasions when an item has been uploaded in error or has been deemed to be commercially or otherwise sensitive.

If you believe that this is the case for this document, please contact UBIRA@lists.bham.ac.uk providing details and we will remove access to the work immediately and investigate.

Harnessing the patient voice in real-world evidence: the essential role of patient-reported outcomes

Melanie J. Calvert, Daniel J. O'Connor, Ethan M. Basch.

Real-world evidence (RWE) is increasingly valued by regulators and payers but importantly can also inform meaningful discussions between clinicians and patients regarding the treatment experience. Central to this evidence base is patient-reported outcome (PRO) data describing the impact of drugs on quality of life, activities of daily and symptoms. Here, we highlight key challenges with current PRO RWE and describe collaborative next steps for international stakeholders to overcome these issues.

Advances in health informatics infrastructure and capabilities for analysing complex large datasets bring opportunities to better characterize the experiences of patients during usual care. RWE data sources include electronic health records, insurance claims and billing, registries, or on site medical chart review. Often missing from these data sources is information about how patients feel and function, as captured directly from patients themselves.¹ As pressures from legislation, international regulatory authorities, and patient groups promote more patient centric drug development and evidence generation,² attention is now turning to the role of PROs to provide the patient perspective in real world datasets.

By definition, PROs represent health status as reported directly by the patient, without interpretation by a clinician or anyone else.² PROs are collected via questionnaires that elicit information about symptoms, physical functioning, and/or health-related quality of life. Historically, most PRO collection has occurred in prospective randomised clinical trials, to inform regulatory decision-making, health technology assessment, reimbursement, and clinical practice guidelines.

Current challenges in PRO real-world evidence

In real world contexts, prospective PRO collection has been limited and fragmented to date, with PROs collected in only 14% (n=8/57) of recent post authorization safety studies, consisting largely of one-off registries for post-marketing assessment sponsored by drug manufacturers in specific populations.¹ Secondary sources of real world data such as electronic health records and insurance claims often do not capture PROs. Even in rare cases when PRO data are collected as a part of routine care delivery, PRO objectives are often not clearly defined, the items collected are not consistent across the same patient group in different regions and the terminologies and timings of assessments are not standardised. This may hinder the integration and interpretation with other data sources, resulting in a missed opportunity for learning more about therapeutic interventions and the overall patient experience.³

Mandated approaches to PRO collection for audit and benchmarking purposes, such as the UK PROMs initiative, have been an important first step in attempting to assess patient-centred health gain within the NHS. However, to ensure full integration of PROs there is a need to improve the efficiency of the data collection, develop guidance on how best to interpret and utilise the data and gain 'buy in' from clinicians and patients regarding the added value.⁴ PRO data collected in a real-world setting needs to generate benefits for patients and clinicians for broader benefits to be fully realised.³

Without PRO data, RWE will not actually reflect how real patients experience real therapies in the real world. And for these data to be useful, standardization of methods for PRO collection, analysis, and reporting is essential - as is availability of standard PRO data collection tools.

Vision and Strategic Priorities

Our vision is to ensure high quality, systematic collection of real-world PRO data that can meaningfully inform patient-centred drug development throughout the product lifecycle. The opportunity to benefit patients, healthcare professionals and society is substantial. In early phases of development, real world PRO data can provide evidence of the burden and natural history of disease, supporting the selection of the most appropriate primary and secondary endpoints for trials. PROs in early access and compassionate use schemes can provide additional complementary insights pre-licence to the clinical trial data and help protect patient safety with PRO alerts. Post authorization, PROs can offer data on long-term tolerability, safety and effectiveness in populations that are more representative than preapproval trials, impacting clinical decision-making and guideline development, and supporting managed access programs e.g. for novel drugs, such as advanced therapies, with high up-front costs but long-term treatment effects, demonstration of the lifetime effects of therapy will play an important role in reimbursement. Real world PRO data also offer benefits at the individual patient level- offering real-time symptom monitoring and tailoring of care to individual patient needs.^{3,5}

Table 1 shows some key considerations in the design and implementation of PRO programs for real world evidence generation, derived from standard approaches in more established research contexts such as prospective clinical trials and cohort studies. Implementation can be resource intensive, therefore, institutional and ground level support for integration into workflow and technology infrastructure and consideration of who pays for data collection are essential components for success. To optimise PRO RWE we consider the following to be key strategic priorities:

- Ensure international collaboration across multiple stakeholders including patients, caregivers, clinicians, regulators, ethicists, industry, payers, and policy makers to agree a standardised approach to assessment.
- Develop a comprehensive standard set of recommendations, methods and tools that are applicable to PRO RWE generation in different settings. Such recommendations should be applicable to both primary data collection in prospective registries and secondary data from electronic healthcare records.
- Formulate a clear governance process for PRO RWE generation including an ethical framework for how patients should be consented, who selects patients, who can access data and how data will be used.³
- Establish standard sets of PRO measures, electronic tools, and administration schedules to raise the bar; there are ongoing efforts (e.g. FDA exploring a common PRO assessment strategy, the European Union Innovative Medicines Initiative (IMI) GetReal project).
- Develop and use electronic PROs wherever possible.
- Minimize workload and technical complexity for patients, clinicians and health providers.
- Carefully consider the objectives of PRO assessment, the timing of assessments, length of follow up, minimization of missingness, and inclusion of patients from diverse backgrounds.⁶
- Ensure data collection adheres to the FAIR guiding principles for scientific data management and stewardship (findable, accessible, interoperable, reusable).
- Provide guidance on how to interpret and use the data.
- Ensure patients and clinicians gain value from assessment through real time access to PRO data to tailor care to individual needs.^{3,5}

In summary, PROs represent health status as reported directly by the patient and offer the potential to capture how a patient feels and functions during their usual care, providing information that is useful to the patient themselves with regards to treatment choices, to the healthcare professional and health service provider. Without PRO data, RWE will not reflect real treatment experiences and such data should be considered across the whole of drug life cycle. However, there is a need for greater standardisation and we have identified a number of key considerations in the design and implementation of PRO programs for RWE generation. Incorporation of RWE in regulatory decisions, clinical practice guidelines, and health policy is still nascent. But as momentum increases and aggregated clinical data become increasingly available for RWE, attention should turn to increasing international collaboration, developing the required tool kit and consistently complementing these real world data with PROs.

Table 1: Key design considerations for collecting patient-reported outcomes for real world evidence generation

Design element	Considerations
Objectives	Clear objectives should be determined as to why PRO data are being collected. This should be informed by existing evidence where available (e.g. evidence from trials, meta-analyses or RWD)
Patient population	Patient population should be defined by inclusion - exclusion criteria
Instrument selection / tool box	The questionnaire(s) used to collect the data should be relevant and valid for the objectives, and the population of interest and meet stakeholder needs. Questionnaires should have been developed with patient input. Language availability, patient acceptability/burden, permissions and fee for use should also be considered.
Frequency of administration	Frequency will depend on stakeholder needs and the study population. Patients with high symptom burden may require more frequent monitoring.
Mode of administration	The data collection plan should outline the permitted modes of administration (e.g. paper, telephone, electronic, other).
Data collection method / source data	Consider primary or secondary collection. Feasibility and resources to support data collection, existing registries, electronic health records, requirement for bespoke collection. Specify management strategies to minimise missing data and bias. Methods to ensure quality control. IT infrastructure may be based on existing system or customised / commercial products.
Monitoring of data	Whether PRO data will be monitored and used to directly inform patient care. ^{5,6}
Presentation of results	The data should be analysed and reported appropriate, in accordance with the prospective described objectives and the instrument recommendations, leading to robust conclusions considering potential sources of bias / confounding.
Ethics	The requirement for ethics approvals should be consider early in the proposals for data collection, following engagement with the health authorities
Data ownership and consent	Contact and agree with health authorities / registry owners
Audit	Mechanisms for on-going audit of data quality etc should be considered
Privacy	Safe guarding privacy and confidentiality of the data
Clinician feedback	Consider the need for PRO alerts, mechanism to feedback concerning results with potential to integrate into patient management pathway
Patient feedback	Consider if patients will be able to review PRO results and use these data to actively participate in decisions regarding their care.

Healthcare provider feedback	Potential to integrate into managed access programmes, etc
Drug manufacturer feedback	Flag to manufacture emerging trends on tolerability and effectiveness in different populations
Regulatory authority feedback	Support safety reporting, post authorisation marketing commitments, long-term activity data
Resources	Determine who pays for license fees, training, data collection, clinic time, device costs etc

Refs 2-6

References

1. Engel, P. et al. Lessons learned on the design and the conduct of Post-Authorization Safety Studies: review of 3 years of PRAC oversight. *Br. J. Clin. Pharmacol.* **83**(4):884-893 (2016)
2. Kluetz, P.G., O'Connor, D.J., Soltys, K. Incorporating the patient experience into regulatory decision making in the USA, Europe, and Canada. *Lancet Oncol.* **19**: e267–74 (2018)
3. Calvert, M. Et al. Maximising the impact of patient reported outcome assessment for patients and society *BMJ* **364** :k5267 (2019)
4. Kyte, D. et al. Reflections on the national patient-reported outcome measures (PROMs) programme: Where do we go from here? *Journal of the Royal Society of Medicine*, **109**(12), 441–445 (2016)
5. Basch, E. Patient-Reported Outcomes — Harnessing Patients' Voices to Improve Clinical Care. *N. Engl. J. Med* **376**:105-108 (2017)
6. Calvert, M. et al. Guidelines for Inclusion of Patient-Reported Outcomes in Clinical Trial Protocols: The SPIRIT-PRO Extension. *JAMA.* **319**(5):483–494 (2018)

Funding and COI

MC is director of the Centre for Patient Reported Outcomes Research at the University of Birmingham receives funding from the NIHR Birmingham Biomedical Research Centre, the NIHR Surgical Reconstruction and Microbiology Research Centre at the University Hospitals Birmingham NHS Foundation Trust, Health Data Research UK, Innovate UK, Macmillan Cancer Support and PCORI. DO is a UK government employee of the Medicines and Healthcare products Regulatory Agency (MHRA), UK. EB is an employee of the University of North Carolina, receives research funding from the US National Cancer Institute and Patient-Centered Outcomes Research Institute, is on the Board of the American Society of Clinical Oncology, Associate Editor for JAMA, and a scientific advisor to CareVive, Sivan, and Self Care Catalysts.

This publication reflects the views of the individual authors and should not be construed to represent official views or policies of UK Medicines and Healthcare products Regulatory Agency (MHRA), the NHS, the NIHR, the Department of Health or UK Government. MC has received personal fees from Astellas, Takeda, Glaukos and Merck outside the submitted work. All authors are members of the SPIRIT-PRO, SISAQOL and PROTEUS consortia.