Review of Patient-Reported Outcome Measures (PROMs) in Clinical Trials of Rare Diseases

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Background

A patient-reported outcome measures (PROMs) is a measurement of the status of a patient's health conditions that come directly from the patient.[1] PROMs include but are not limited to Health Related Quality of Life. They are most commonly used in clinical trials of products that are used for chronic, disabling conditions where the goal of the treatment is to improve symptoms, functioning and quality of life.[3] PROMs have the potential to systematically incorporate patient perspectives to measure those outcomes that matter most to patients.[2]

Whilst PROMs are not a new idea, their uptake in the research community has been slow and laborious. Most current clinical research and practice falls short of this objective by selecting outcome measures which do not capture patient value to the fullest.[2]

Rare diseases pose a unique challenge to clinicians and researchers because of their low prevalence, establishing the impact of potential treatments is difficult. When sample sizes are necessarily limited, high instrument responsiveness (i.e., the ability to detect all important effects, even if small) is particularly important.[4]

Routinely using PROMs have shown to improve patient satisfaction with their care, symptoms management, quality of life and survival rates. PROMs help to promote patient centered care by improving communication between clinicians and patients about disease states and progression of the patient's disease state.[2]

Objective

The objective of this study is to provide a review of the value of patient-reported outcome measures in clinical trials of rare diseases and to identify the percentage of clinical trials which incorporate PROMs that affect patient lives the most and improve quality of life.

Method

A search of existing literature, including abstracts, published in the PubMed database from 2015 to 2018, was conducted identifying studies that show the importance of outcome measures which captured the patient perspective associated with patient reported outcomes. Keywords used for search include: rare diseases, rare disorders, PROMs, clinical trials, quality of life.

Identification of rare diseases, defined as a disease with a global average of 40 cases/100,000 people, was evaluated in the ISPOR Rare Disease Special Interest Group. Using Orphanet Report Series, top twenty rare diseases were selected for further evaluation, such as Congenital Cytomegalovirus, 22q11.2 Deletion Syndrome and others (see Results). Clinicaltrials.gov was accessed to identify active, not recruiting clinical trials and primary and secondary outcomes were collected. Each outcome measure was assessed to find outcomes that were used to measure change in general health status, acute and chronic pain, and depression while waiting for care and after surgical treatment, etc. that were reported directly by the patient.

PROM data from the clinical trials for the identified rare diseases was collected and evaluated. The number of clinical trials that use PROMs for each disease state and selected therapeutic areas were calculated as well as the average number of PROM used in each clinical trial.

Results

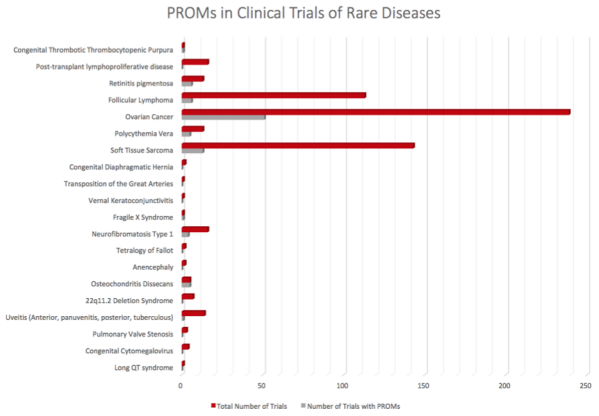

Fig. 1. Total number of clinical trials reviewed and number of trials with PROMs

- There were a total of 612 clinical trials reviewed from the 20 rare diseases that were chosen. From 612, there were a total of 92 clinical trials that used patient-reported outcome measures as primary or secondary endpoints (Fig.1).
- Approximately 15.03% of the clinical trials used PROMs.
- On average, 1.8 patient reported outcomes were used in each clinical trials.
- Reviewed oncology studies included Neurofibromatosis Type 1, Soft Tissue Sarcoma, Polycythemia Vera, Ovarian Cancer, Follicular Lymphoma and Post-transplant lymphoproliferative disease. Evaluation of these clinical trials showed that only 14.74% of oncology clinical trials are utilizing PROMs (Fig. 3).
- Reviewed cardiology studies included Long QT syndrome, Pulmonary Valve Stenosis, Tetralogy of Fallot and Transposition of the Great Arteries. None of the cardiology studies utilized PROMs (Fig. 4).
- Reviewed ophthalmology studies included Uveitis (anterior, panuveitis, posterior, tuberculous), Vernal Keratoconjunctivitis and Retinitis pigmentosa. Evaluation of these clinical trials showed that 21.43% of ophthalmology clinical trials are utilizing PROMs (Fig. 5).
- Ophthalmology studies show the highest percentage of PROMs presented in primary and secondary outcomes measures within three therapeutic areas presented in this research.

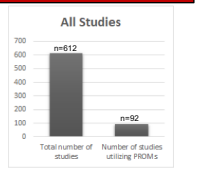

Fig. 2. Overall number of studies utilizing PROMs

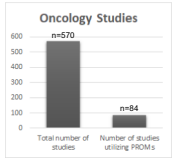

Fig. 3. Number of studies utilizing PROMs in reviewed oncology studies

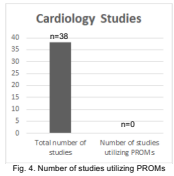

Fig. 4. Number of studies utilizing PROMs in reviewed cardiology studies

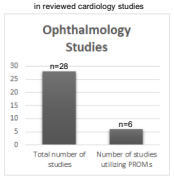

Fig. 5. Number of studies utilizing PROMs in reviewed ophthalmology studies

Limitations

- Represented research includes the whole range of clinical trial phases (I-IV). Phases I and II of clinical trials are mostly focused on safety of a new drug and designed to evaluate pharmacokinetics and pharmacodynamics of the drug, establish maximum tolerable dose and see possible adverse events. However, in this study we didn't distinguish between phases and evaluated all primary and secondary outcomes. For future studies, this research should solely be focused on phases III-IV clinical trials as they evaluate efficacy of the drug in real patients who can provide PROMs.
- Reviewed ophthalmology therapeutic area had only 28 ongoing clinical trials, thus the percentage of PROMs used can seem much higher compared to other therapeutic areas that had more ongoing trials.

Conclusions

Rare diseases can lead to a significant reduction in quality of life for patients and their families. Ensuring the patients voice is central to clinical decision making is key to delivering, evaluating and understanding the efficacy of therapeutic interventions. Patient reported outcome measures (PROMs) are used to capture the patient's views about their health status and facilitate our understanding of the impact of these diseases and their treatments on patient's quality of life and symptoms.[3]

Based on the literature search and the overview of clinical trials in rare diseases, we identified that PROMs were not measured in the majority of clinical trials. Literature review demonstrated support for using PROMs in clinical trials to better understand the effect of the treatment on patient symptoms and quality of life. Previously, only measurable outcomes such as labs and mortality rates, were used. Even though such outcomes were easily quantifiable, they were not an accurate representation of the patient experience. Difficulty with technological and operational barriers may be some of the reasons hindering the incorporation of PROMs into clinical trials. It is important for healthcare systems to start integrating PROMs into patient care in order to provide better well-rounded treatment.

Only 20 rare diseases were reviewed based on their prevalence. A larger scale research or research focused on a single therapeutic area would be able to provide more thorough overview of PROM utilization in clinical trials.

Resources

1. Jaroslawski, S., Auquier, P., Borissov, B., Dussart, C., & Toumi, M. (2018). Low rates of patient-reported outcome claims for orphan drugs approved by the us food and drug administration. *Journal of Market Access & Health Policy,6*(1), 1433426. Retrieved March 30, 2019.
2. Morel, T., & Cano, S. J. (2017). Measuring what matters to rare disease patients – reflections on the work by the IRDiRC taskforce on patient-centered outcome measures. *Orphanet Journal of Rare Diseases, 12*(1).
3. Slade, A., Isa, F., Kyte, D., Pankhurst, T., Kerecuk, L., Ferguson, J.,Lipkin, G., Calvert, M. (2018). Patient reported outcome measures in rare diseases: A narrative review. *Orphanet Journal of Rare Diseases, 13*(1). Retrieved March 20, 2019.
4. Johnston, B., Millaer, P., Agarwal, A., et.al. (2016). Limited responsiveness related to the minimal important difference of patient-reported outcomes in rare diseases. *Journal of Clinical Epidemiology*, 79 (10-21). Retrieved March 30, 2019.

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