
The Growth of Phase IV Trials and the Need to Demonstrate Effectiveness Using Electronic Patient Reported Outcomes

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Introduction

Patient centricity is now at the forefront of drug development, from early understanding of Burden of Disease through to Comparative Effectiveness Research and the use of Real World Data to generate evidence on the patients' perspective of outcomes and quality of life. With the rise in patient centricity, we see the growth for the need of Patient Reported Outcomes (PRO) and associated technologies allowing these outcomes to be collected and leveraged to meet the needs of multiple stakeholders including Patients, Patient Advocacy Groups, Payors and Pharma.

Rapid growth in the development of innovative therapies and medicinal products over the past several decades has seen a rise in the development of Advanced Therapy Medicinal Products (ATMPs), including Gene and Cell Therapies as well as other complex molecules, and with this there has been fast changes to regulatory requirements. Today, convincing regulators of a product's safety and efficacy to obtain marketing authorisation is no longer the only barrier to ensuring accessibility to medicines for patients.

Pharmaceutical companies must now satisfy the value perceptions of multiple stakeholders, including payers, to attain market access for products. Regulatory approval is an essential and necessary step in market authorisation, but Market Access is no longer guaranteed¹. This paper therefore seeks to address and describe the growing need to satisfy the value perception of multiple stakeholders and the importance of Late Phase trials capturing Clinical Outcome Assessments (COA) and specifically electronic Patient Reported Outcomes (ePRO) in relation to this.

Patient Centricity

Today, digital technologies are available to many and patients are increasingly being informed about their conditions and possible treatments through apps, social media and patient internet forums. With greater attention and understanding of the importance of patient centricity to help ensure successful Market Access, Patient Reported Outcomes are now playing an increasingly prominent role. As patient involvement continues to be acknowledged as an integral factor in the success of a product, the patients' perspectives are increasingly required or included during the lifecycle of the product and from the early phase of product development² through to authorisation and post- marketing. Payors and providers are seeking closer relationships at an early stage with pharmaceutical and biotech companies and want to see the generation of evidence that show therapies address the health problems patients face on a daily basis³.

Various initiatives exist which aim to increase patient involvement and engagement in the drug development process, including the PREFER and PARADIGM project under the Innovative Medicines Initiative (IMI)⁴. The need to capture the patients' perspective throughout the lifecycle of a product is more widely understood and appreciated than ever before.

In terms of providing patients with products quickly and that meet their healthcare needs, the aforementioned regulatory and reimbursement hurdles together with efforts to utilise harmonised frameworks and methodologies means progress is still needed, given 'a one size does not fit all'. With this in mind, the functions of Medical Affairs, HEOR and Market Access are taking a prominent seat at the table.

1 <https://pharmaphorum.com/views-and-analysis/overcoming-the-market-access-hurdle-through-better-planning-of-clinical-trials/>

2 Sendyona S, Odeyemi I & Maman K, Perceptions and factors affecting pharmaceutical market access: results from a literature review and survey of stakeholders in different settings, *Journal of Market Access & Health Policy*, 2016, 4:1, 31660

3 http://www.pmlive.com/pharma_intelligence/Integrating_patient_reported_outcomes_into_clinical_trials_1312271. 2019

4 Lowe MM, Blaser DA, Cone L, et al. Increasing patient involvement in drug development. *Value Health* (2016) 19:869–78. 10.1016

Late Phase - Real World Evidence (RWE)

Healthcare stakeholders including regulators and payors are continually moving toward Real World Evidence (RWE) to complement evidence from randomised controlled trials⁵. Phase IV prospective trials collecting PRO data can be used to inform, increase understanding and add value to stakeholders decision making and collecting this PRO data electronically (ePRO) offers significant advantages over paper collection. The shift from paper-based to ePRO data capture is encouraged by regulators given the enhanced integrity and accuracy of the clinical trial data⁶. Furthermore, with the availability of Bring Your Own Device (BYOD) to collect RWE within late phase studies, subjects can participate with the familiarity of their own devices, whilst representing a cost-effective solution for sponsors. Technologies which reduce burden for patients and allow them to easily participate in late phase trials can aid in engaging and retaining the patients throughout the study and with the availability of virtual solutions including remote eConsent and telemedicine, individuals can quickly and effortlessly enroll within a study without travelling to the site.

Phase IV studies typically seek to understand the real-world effectiveness of a drug as evaluated in an observational, non-interventional trial in a naturalistic setting. They can be mandatory requirements imposed by Regulatory Authorities such as a Post Authorisation Safety Study (PASS) through the EMA and Risk Evaluation and Mitigation Strategy (REMS) through the FDA or voluntary initiatives by pharma to collect RWE in order to understand the therapeutic potential of a drug once it has been approved, to explore new formulations, new indications, adherence and potentially other patentable innovations⁷.

The use of Real World Data (RWD) to generate RWE and specifically patient insights, can help inform decision making throughout the lifecycle of a product, from early on in the drug development process through to post authorisation. Using RWD and specifically Phase IV studies as a means to collect electronic Patient Reported Outcomes prospectively can offer many advantages over other methodologies of analysis such as Retrospective studies. For example, Retrospective studies may be prone to recall bias or misclassification bias and some key statistics cannot be measured in this kind of experimental design⁸. Retrospective data analysis can be fragmented and heterogeneous and often may not take into consideration the voice of the patient. In contrast, ePRO allows us to ask specific questions pertaining to the patient's own journey and give an important insight into their perceived quality of life.

Wearable Technology

A further benefit of prospective data collection in a late phase trial over a retrospective study is the availability of wearable technology (sensors) to monitor and collect health-related data remotely. The benefits of utilising such sensors within a late phase study are becoming widely recognised and with the rapid rise in wearable technology, their usage *in-situ* is increasing.

5 Khosla S, White R, Medina J et al, Real world evidence (RWE) – a disruptive innovation or the quiet evolution of medical evidence generation? F1000 Res. 2018; 7: 111.

6 Coons SJ et al, Capturing Patient-Reported Outcome (PRO) Data Electronically: The Past, Present, and Promise of ePRO Measurement in Clinical Trials, Patient. 2015; 8(4): 301–309.

7 <https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/phase-iv>

8 <https://litfl.com/retrospective-studies-and-chart-reviews/>

Wearables can provide objective measures of traditionally subjectively reported outcomes, such as pain, fatigue or mobility as a measure of quality of life, complementing patient reported outcomes. The passively collected data for a person's physical activity and movement from a sensor can interact directly with devices such as smartphones via Bluetooth and together with ePRO can transfer to a secure data store capturing this health-related information. With additional data being collected such as mobility, vital sign data as well as data pertaining to adherence, timely interventions by clinicians and caregivers can be made, if required.

Capturing this data together with PROs, allows a deeper understanding at the patient level, with both the subjective and objective collection of data. Historically there were no well-developed standards that would help to organise and standardize the data and provide data mapping tools to electronic data capture (EDC) databases⁹, however with rapid technological advances and an industry leading EDC platform, data can be unified offering immediate insights of the patient in real time¹⁰. Moreover, as we move toward greater virtualisation within clinical trials - now heightened with response to the COVID-19 pandemic, the requirement for at-home use of wearable technology increases, together with remote consent and remote visits in the form of telemedicine.

Outcome-Based Agreements

An important attribute of challenges we face in the healthcare industry is the affordability challenge and it has been remarked that affordability is the key to accessibility¹¹. Innovative products are now treating diseases that only in the recent past did not have viable treatments. But with these new products come higher manufacturing costs, increased spending in Research & Development and ultimately higher costs of healthcare. Patient associations have also become more active and are able to lobby for public funding of often costly curative treatment¹², as well as pushing for innovative treatments for under-served diseases.

Given the requirement for novel therapeutics, patient insights, the changing healthcare landscape, the importance of Market Access and RWE, it has been remarked that the historically, widely used model of volume-based fee-for-service reimbursement is unsustainable. We are now seeing that outcomes-based reimbursement models have become increasingly common over the last decade or so in markets such as the US, Europe and Australia¹³. Outcome based models of reimbursement may provide many benefits, addressing the affordability challenge, reducing risks for payors and improving outcomes for patients¹⁴.

As the industry moves towards personalised, outcomes-based care with the shift from volume-based fee-for-service reimbursement to Outcome-Based Agreements, the need to show effectiveness and how the drug is performing in the real world is therefore becoming increasingly important.

9 Izmailova E, Wagner J, Perakslis E, Wearable Devices in Clinical Trials: Hype and Hypothesis, *Clin Pharmacol Ther.* 2018 Jul; 104(1): 42–52.

10 <https://www.medidata.com/en/unifythecore/>

11 Shaw K, Leveraging affordable innovation to tackle India's healthcare challenge, Volume 30, Issue 1, March 2018, Pages 37-50

12 Sendyona S, Odeyemi I & Maman K, Perceptions and factors affecting pharmaceutical market access: results from a literature review and survey of stakeholders in different settings, *Journal of Market Access & Health Policy*, 2016, 4:1, 31660

13 <https://pharmaboardroom.com/articles/shooting-for-the-stars-the-evolution-in-outcome-based-payment-models-for-medicines/>

14 <http://www.smf.co.uk/wp-content/uploads/2017/07/Data-for-Outcomes-final.pdf>

Relative Effectiveness can be defined as: "the extent to which an intervention does more good than harm compared with one or more alternative interventions under the usual circumstances of healthcare practice". The success of the product on the patient to achieve positive outcomes can be affected by many factors. Such factors can include Biological Factors: Severity of Disease, Genetics, Sex and Co-morbidities. Behavioral factors can include: Adherence to Disease Management Plans, Lifestyle and Socioeconomic factors.

With regard to the Increase in Outcome-Based Agreements in reimbursement, historically performance metrics did not incorporate patient reported measures and relied on objective data only - the number of rehospitalisations, recurrence of cardiac events etc. The use of PRO in this regard historically faced challenges, for example provider buy-in, resource investment and that practical data collection was challenging. This is changing with the growth of technologies including electronic completion, collection and reporting of data allowing the patients' voice to be heard.

Patient Reported Outcomes are now providing a direct reflection of reimbursement, playing an intrinsic role as we have seen in November 2019 with the value-based agreement with Biogen for Tecfidera® (dimethyl fumarate) and Avonex®, linked to MS patient-reported measures of disability progression in a real-world population.¹⁵

As Payors continue to seek closer evidence-based relationships with pharma, to understand the true value of a product, the patients' voice is being given increased importance in decision making and willingness to pay. It is therefore of value to all stakeholders to ensure, with relation to the factors regarding effectiveness, that all is being done to ensure patients can achieve successful outcomes – the outcomes important to them. As Janet Woodcock, Director of the Center for Drug Evaluation and Research at the Food and Drug Administration, said in 2015. "It turns out that what is really bothering the patient and what is really bothering the doctor can be radically different things".

Adherence

When considering behavioral factors such as adherence, Phase IV trials can be used to identify and understand patient adherence. The effectiveness of any drug is reliant on patients accurately following instructions.

An example of this would be from a survey on adherence to Glaucoma medication which showed that 50% of people diagnosed with glaucoma were found to be risking blindness by not adhering to their regimen 75% of the time. The reason for the poor adherence was said to be that the eye drops were difficult to administer¹⁶.

In the US, hospital admissions due to poor drug regimen adherence alone are estimated to cost \$100bn a year¹⁷. By providing patient insights through ePRO and by identifying potential barriers to patient adherence and gaining insights from the patients themselves, any potential obstacles can be understood and overcome. Increasing adherence and successful patient outcomes by gaining insights into the patients' perspective through Patient Reported Outcomes, will ultimately aid in the improvement of effectiveness which can be demonstrated in a Phase IV study, using ePRO.

15 https://www.upmchealthplan.com/pdf/ReleasePdf/2019_11_14.html

16 Okeke CO, Quigley HA, Jampel HD, et al. Adherence with Topical Glaucoma Medication Monitored Electronically, Ophthalmology. 2009 Feb;116(2):191-9

17 Osterberg L and Blascke T, Adherence in Medication, N Engl J Med 2005;353:487-97

Comorbidities

Insights reported directly from patients in Phase IV studies could help understand the environment for which a patient belongs, in terms of what other medications they are taking, how often and what current adverse events, if any, they experience.

A speech in Q4 2019 by a senior NHS Chief, Sir Munir Pirmohamed at the House of Lords Science and Technology Committee meeting, shared that 6.5 percent of patients at hospitals in the United Kingdom were admitted because of drug reactions, costing the NHS £1.6 billion. A key factor mentioned was that older patients can be prescribed between ten and 20 types of medication at once, which can lead to the risk of adverse effects when drugs interact with each other. But given that clinical trials may not include over 65s, this data is often not being accounted for in the drug's safety and efficacy data prior to approval.

When considering chronic disease, about half of US adults, or 117 million individuals, have at least one chronic disease¹⁸, according to 2012 data from the Centers for Disease Control (CDC). Chronic illness accounted for approximately 86 percent of healthcare spending in 2010, the CDC says. Those costs are further increased by almost 80 percent of patients who fail to adhere to their chronic disease management programs¹⁹.

Improving non-compliance is a top priority for clinicians – and understanding from the patient perspective using ePRO in a Late Phase study can help understand and improve adherence in the long term. Furthermore, the discussion and understanding of the benefit of Patient Support Programmes is increasing and may be a mechanism to aid in the success of adherence and therefore successful patient outcomes.

Quality of life (QoL)

In the UK, NICE evaluates the drug in terms of extension of life and Quality of Life (QoL) improvements which is set against cost. NICE technology appraisal recommendations are prepared by an independent advisory committee - the Technology Appraisal Committee - evaluated where the cost of a Quality Adjusted Life Year (QALY) is below cost-effectiveness thresholds²⁰.

The importance of measuring the impact of a treatment on a person's QoL and emotional well-being has been frequently reinforced by patients with severe diseases. It has been emphasized by patient advocacy groups the added value of just a few months of life for patients with severe diseases, as it allows them the ability to see their grandchildren and spend time with their family, even if this doesn't fit with the typical QALY definitions.

This may include holding increased importance on more modest extensions to life expectancy where these have a greater impact on the QoL of the patient or where life expectancy is otherwise very short²¹. Understanding what the most valuable impacts are for patients should come directly from the patients' perspective to ensure their voice is being heard and may play a significant role in willingness to pay and recommendation of reimbursement from Health Technology Assessments (HTA). Moreover, collecting this QoL data in a real-world setting may demonstrate the true value an authorised product brings to that patient population and thus the need to show QoL through Late Phase studies is greater than ever before.

18 <https://health.gov/dietaryguidelines/2015/guidelines/introduction/nutrition-and-health-are-closely-related/>

19 <https://patientengagementhit.com/news/why-do-patients-quit-chronic-care-self-management-programs>

20 NHS England, Appraisal and Funding of Cancer Drugs from July 2016 (including the new Cancer Drugs Fund), (2016)

21 https://prostatecanceruk.org/media/1633387/value-based_pricing_report_final_for_print.pdf

Summary

As we see an increase in patient centricity with the industry focusing on the benefit of the empowered, informed and motivated patient, the patients' voice continues to grow as an integral factor to ensure Market Access and successful patient outcomes in the real world. By generating this data in a Late Phase study in a real world setting through ePRO as well as other wearable technologies, the ability to increase effectiveness can be understood, enhanced and ultimately the gap between relative efficacy in the clinical trial and relative effectiveness in the real world, can be bridged, resulting in the value perception of all stakeholders being met.

Adam Levy is a mHealth Solution Specialist at Medidata. If you would like to discuss any of the aspects or technology discussed within this paper, including BYOD, wearables, virtualization, a unified platform or (remote) eConsent, please reach out for a discussion with the author on how these technologies can be adopted for your study.
