Worldwide Clinical Trials

4P Medicine: Prevention, Prediction, Precision, & Participation and Its Impact in Clinical Development

Lissenya B. Argueta, PhD: Fellow, Clinical Research Methodology

Michael F. Murphy, MD, PhD: Chief Medical & Scientific Officer

Worldwide Clinical Trials | May 2024

Introduction

The integration of Patient-Reported Outcomes (PROs) into medical research has garnered increasing attention, exemplifying the potential to shape personalized healthcare across four distinct dimensions: predictive, preventive, personalized, and participatory medicine, together known as "4P medicine" — a concept in development and refinement over the last 15 years.[1] The combined ability to prevent disease, predict who might be at risk or respond to treatment, create a personalized treatment strategy, and entice patient participation present significant insights for drug development. Although these data are typically interpreted by a clinician, at the core, patient perspectives integrate into an overarching treatment plan, thus allowing tailored treatment plans to individual patients where the patient has been an active participant. Applying the principles of this 4P approach informs researchers, payors, and patients alike, directly impacting the scope and detail of a clinical development program for investigational agents.

Systems medicine: Extending beyond a genetic substrate

Across numerous diseases, evidence indicates substantial individual variations in the molecular foundations of disease susceptibility and its progression. For instance, extensive investigations illustrate the genetic influence on conditions such as obesity, asthma, type 2 diabetes, and cardiovascular disease.[3] Systems medicine takes a holistic approach, incorporating various biological data sources such as DNA, RNA, proteins, metabolites, small molecules, and the interactions of cells and organs. It extends this information to consider individuals embedded within social networks, integrating these diverse elements to develop predictive and actionable models for health and disease.[4] These concepts provide an overarching framework for considering predictive, preventive, participatory, and personalized implications.

Prediction of Disease Susceptibility/ Treatment Responders

Exploring biological pathways influenced by genetic predispositions has the potential to revolutionize healthcare. A foundational understanding of systems biology provides insight into populations more susceptible to developing certain diseases. The interplay of systems biology and pharmacology potentially enables identifying responders before treatment. Identifying patients vulnerable to specific adverse events (AEs) enables healthcare stakeholders to focus on preventive measures or the delivery of tailored interventions.

For example, pharmacogenetic testing before drug administration to predict and potentially avoid AEs may reduce patient reluctance to take medications while also empowering providers with greater confidence to prescribe.[6] The costs and benefits of developing and implementing pharmacogenetics as a predictive tool depend on the clinical situation. Generally, they are

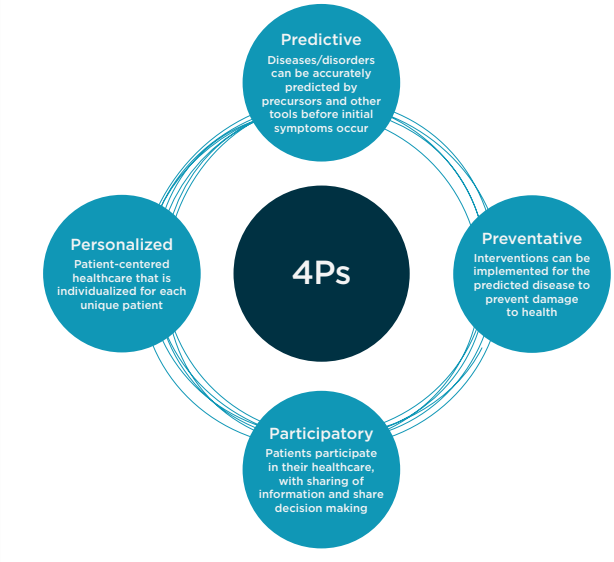

Figure 1. The 4P's defined. A visual schematic depicting the interplay between prediction, prevention, participation, and personalized medicines. (Adapted from Collins 2019).[2]

most efficient and accurate when taking a combined approach, incorporating genetic and environmental factors (e.g., epigenetic modifications) captured in secreted proteins detectable in serum, blood, or other matrices.[3]

These approaches reflect a complex interconnected hierarchy of information, with the environment exerting influence at each level, repeatedly modifying the original genomic signal "epigenetically".[7] Full implementation could extend drug discovery into drug development for early phase investigations under a "fit for purpose" biomarker development program in which an array of fluid, electrophysiological, and neuroimaging biomarkers support clinical research hypothesis generation.[8]

Predictive modeling, in part based on genetic or biomarker signatures, creates an ability to segment patients into those with a higher probability of a condition, either in a deterministic or probabilistic fashion. It empowers organizations responsible for formulary placement and reimbursement decisions to transition from passive intermediaries in transactions to significant participants in clinical decision-making. Current policy decisions regarding reimbursement and authorization are routinely informed by insights gleaned from aggregated data, such as the proportion of patients achieving clinically significant responses on PROs, and frequently translated into performance-based metrics like the number needed to treat within the confines of a given therapeutic setting.

A predictive modeling algorithm thus could extend the process to a patient level. Precedents exist for evaluating, if not mandating, specific improvements in discrete outcomes for individual patients' post-treatment initiation,[9] reflecting the emerging importance of patient-reported outcomes in oncology as an example.[10] Furthermore, the connections between PROs and economic outcomes, both representative of healthcare outcomes, often remain fragile, even in well-established chronic illnesses like type 2 diabetes, underscoring the need for future payer-sponsored research efforts.[11]

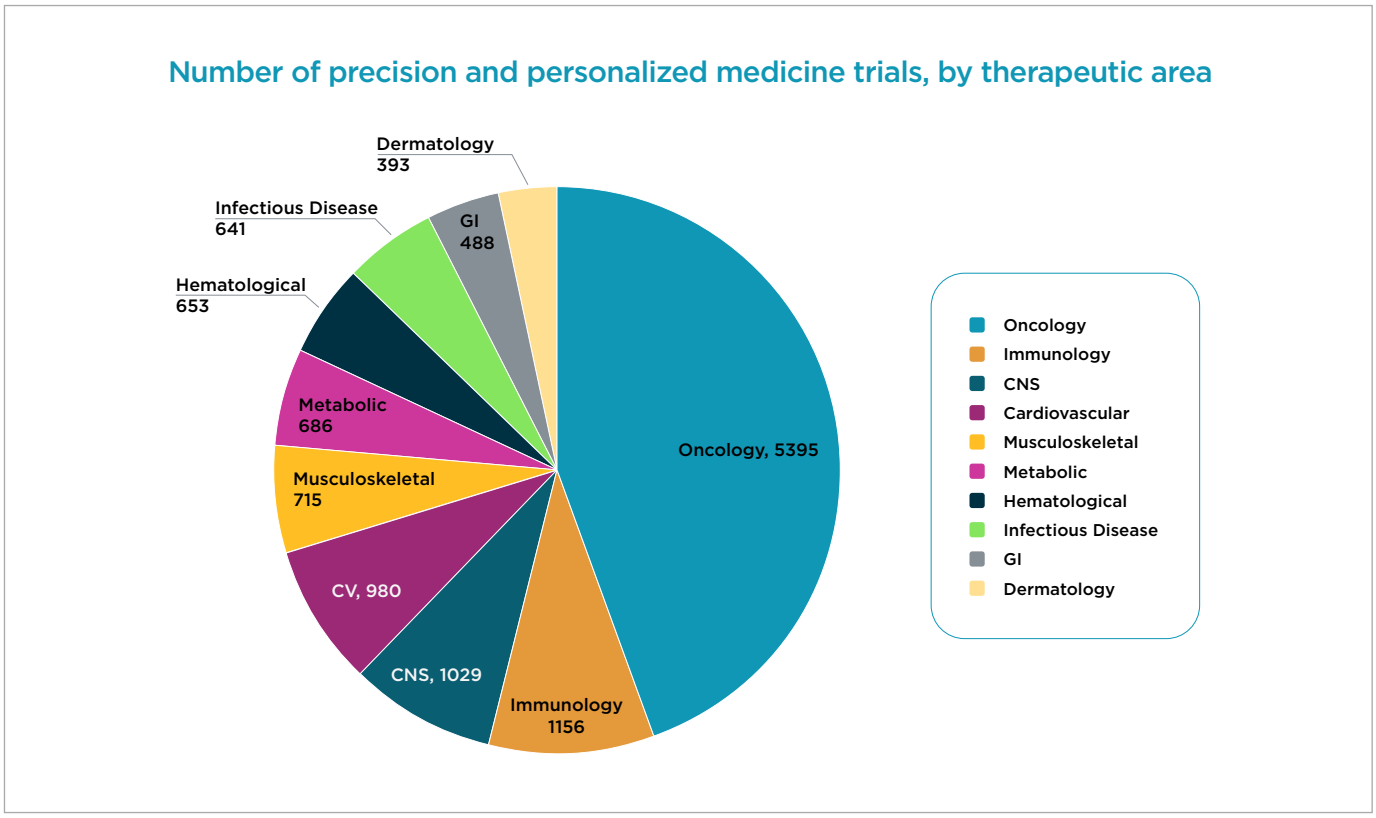

Figure 2. The expansion of 4P Medicine Across Therapeutic Areas. While Oncology currently dominates the field regarding the use of 4P medicine, its implementation is quickly rising in other therapeutic areas (i.e., immunology, CNS, and cardiovascular diseases). Data were acquired from analysis of precision/personalized medicine trials across all therapeutic areas and all phases on the West Coast (US) and globally. (Adapted from GlobalData Pharma Intelligence Center).[5]

Personalized/Precision Medicine: A Catalyst for Innovative Trial Methodology

It is axiomatic that no clinician will treat an average patient. Thus, the unique genetic, demographic, disease phenotype and environmental factors dictating response to therapeutics are unique to each individual. Precision medicine is an emerging field credited to the recent availability of big data, the use of artificial intelligence, and advancements in the "-omics" (e.g., genomics, transcriptomics, and proteomics) to partially address this objective. Numerous efforts are underway to characterize individual differences in molecular processes underlying disease pathogenesis, disease progression, and the response to therapeutics. Once we understand these molecular differences, we can enhance therapeutic development by using the information to identify individuals more likely to benefit from a given intervention strategy. High-throughput genomic technologies already provide the data that will serve as the foundation of personalized medicine. Emerging technologies, including family genome sequencing, proteomics, metabolomics, single-cell analysis, imaging modalities, and the discovery of induced pluripotent stem cells, have all contributed to the advancement of personalized medicine.[7]

Challenges Facing Implementation in Clinical Trial Designs

Incorporating these diverse data points, which may be mediators and confounders of the therapeutic effect, becomes increasingly problematic using conventional trial methodology. Traditionally, these methodologies pivot on an ability to detect an average treatment effect within a relatively homogeneous group of subjects under a supposition that the least biased estimate of a treatment effect in a population sample will be while simultaneously acknowledging dispersion around that estimate within a confidence interval. Accommodating the identification of patient subgroups most likely to benefit from a given therapy is subsumed in the "stratified medicine" concept.

A typical implementation of the stratified medication concept uses alternative covariate-adjusted designs to ensure a balance of treatment assignments across various strata defined by patient-level attributes.[12] Insufficient subject recruitment for these studies frequently, especially when subgroups are of interest, limits the incorporation of necessary covariate information into the design, consequently reducing the precision of treatment effect estimates. Indeed, the single most important challenge facing personalized medicine in designing clinical trials is establishing a robust statistical framework for multidimensional patient-level data analysis.

However, the challenges increase for those agents individually designed for specific patients rather than a group of patients, and traditional approaches for an adjusted analysis are less informative. Regulatory, nonclinical, and clinical challenges associated with this concept are widely acknowledged, and the FDA has formulated a framework for discovery and development activities within personalized medicine.[13] The FDA's Division of Translational and Precision Medicine (DTPM) is emblematic of the need to integrate specialists across diverse disciplines related to regulatory review for evidentiary standards of approval, new regulatory science, and guidance and policy development.[14]

As an example, Therapeutic advances for individualized antisense oligonucleotide (ASO) represent an emerging trend in which labs design individual molecules to target respective patients. The unique challenges associated with this initiative have prompted guidance for the framework of drug discovery and development.[15] Innovative designs such as master protocols thus emerge, incorporating both platform and basket concepts in the case of individualized ASOs to permit systematic evaluation of multiple therapeutic moieties against equally diverse clinical targets under the umbrella of one common protocol, with eligibility that would accommodate different disease phenotypes but with standardized safety requirements.[16]

Patient Participation: Innovative Hypotheses and Unique Measures

The acquisition and access to databases with both the scale and detail to enable patient segmentation and predictive modeling require robust patient participation in an enabling clinical development process with prospectively planned observational and interventional research. Frequently evaluating faciliatory and inhibitory factors for the involvement of patient research allows for the development and offering of tractable activities to incorporate into a clinical development program prospectively.

For example, the physician's role ranks highly among these, as the physician-patient relationship, the reputation of the physician in the community, and the relatability of patients to the physician become paramount. Variables such as gender/sex, race/ethnicity, or familiarity with the same language and customs are all understood as possible motivational contributors to patient participation. The relationship between physician and patient is significant in those illnesses characterized by considerable mortality and morbidity and can be a material factor in patient engagement processes.[17]

Given that a patient/family's willingness to participate in clinical research is a multivariate process, many other factors can potentially influence patient decisions regarding study participation. These include general distrust of medicine, time commitment, study follow-ups, and access to transportation. It is important to ensure patients understand the study properly and will either work in favor or against their participation in a study, depending on how well the information is delivered and understood.

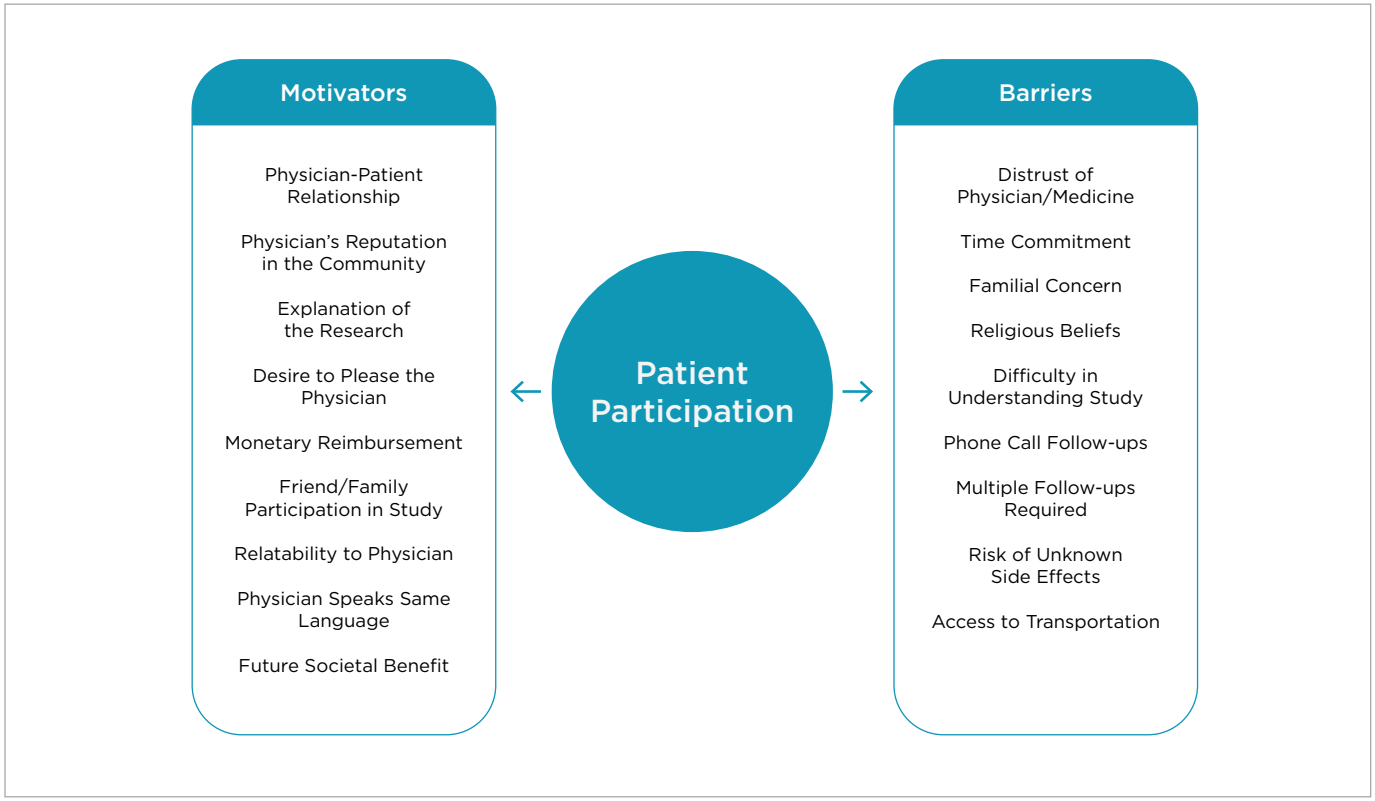

Figure 3. Influential Factors at Play in Patient Participation. Multiple variables can either drive patients towards or away from participating in clinical trials. (Adapted from Gayet-Ageron, Rendez, & Perneger 2017).[18]

Incorporating the Patient's Voice: Patient-Reported Outcomes

Oncology is perhaps the top therapeutic area in which the importance of patient-reported outcomes has been recently emphasized, given the transformative therapies and scientific advancements effectively transitioning a previously lethal disease class to chronic.[10] For example, previously lethal disease entities (e.g., breast cancer and testicular cancer) are now well-managed, with overall survival approximating that of the general population.

Generally characterized as a composite of multiple domains, a patient-reported outcome would sample disease symptoms, symptomatic adverse events, social well-being, emotional well-being, and physical and cognitive function. These assessments' general framework and structure are captured by a series of guidance documents, for example, from the European Medicines Agency and the FDA, extending back well over a decade.[19]

All guidance documents emphasize incorporating patient voice as a prime directive, utilizing either bespoke measures or adaptation of current ones, creating a more expanded concept of "benefit," and attending to special populations such as pediatrics, adolescents, or patients in end-of-life palliative care. An overarching emphasis on attention to methods, analyses, and content is universal.

Instead of receiving care passively, data generated from a patient or caregiver perspective during clinical trials and subsequently in commercial settings can aid in tailoring treatment decisions to individual patient needs. For instance, the widespread presence of PROs on a patient-centered online platform indicates that web-based data entry could serve as a valuable resource for generating hypotheses.[20] The overarching discussions about QOL in personalized medicine are equally relevant to the broader term "PRO" when indicating any health-related report directly provided by the patient.[21] Patient-derived data, frequently captured under the umbrella of a patient-reported outcome, is also often used to determine policy for placement of new agents on formulary and for reimbursement decisions. In addition to the cost of care, physicians and patients can use patient insights when ranking one therapeutic agent against another within the same indication. This is particularly useful when traditional trial-level data offers little distinction between products and may also be incorporated into the process of shared decision support and patient-physician dialogue.[22]

A proposed multivariate framework has emerged, recognizing the limitation of a one-size-fits-all approach in addressing patient-specific differences. While this framework was initially designed for binary outcomes, whether PRO-related or not, it can be tailored to accommodate continuous PRO (and non-PRO) outcomes.[12] The five recommendations comprising this novel framework are listed below in Table 1.

Proposed Framework:
1. Assessment and disclosure of the distribution of baseline risk within the overall study population and across different treatment arms using a risk prediction tool
2. Illustrating differences between relative and absolute changes based on baseline characteristics using a primary subgroup analysis prediction tool
3. Predetermining additional primary subgroup analyses for individual variables, restricting these to patient attributes supported by robust pathophysiological or empirical evidence
4. Differentiating secondary or exploratory subgroup analyses from primary subgroup comparisons
5. Presenting all conducted analyses with a statistical assessment of treatment effect heterogeneity using appropriate methods, such as interaction terms, while exercising caution against overinterpretation

Table 1. Proposed Framework to Evaluate Risk-Based Diversity of Treatment Effects. (Adapted from Alemayehu & Cappelleri, 2012).[12]

Conclusion

At Worldwide Clinical Trials, we understand that every disease has heterogeneity across patients and envision a future in medicine where every patient is treated for their unique needs. The emergence of 4P medicine highlights the importance of leveraging diverse biological data and integrating this information into a societal concept to develop actionable models for patient management and health and disease. Implementation of personalized approaches in the development process necessitates novel clinical trial methodology and analyses within the context of evolving evidentiary product approval standards. Patient-reported outcomes, either modified from existing instruments or created de novo for unique populations, also gain ascendancy in a hierarchy of analyses. An openness to hypothesis generation, particularly in early phase research, unique measures, and awareness of evolving requirements for product registration are key. Design and operational decisions in development thus potentially impact multiple stakeholders, additionally placing a premium on patient and family participation.

Furthermore, a proposed framework for evaluating the inherent heterogeneity in estimating the treatment effect effects emphasizes the need to move away from a one-size-fits-all approach for key patient-reported measures and treatments and instead focus on providing interventions tailored to individual characteristics. Overall, personalized medicine, guided by PROs and incorporating advancements in technology and biological sciences, offers significant potential for enhancing patient care and improving healthcare outcomes.

References

1. Hamburg MA, Collins FS. The path to personalized medicine. N Engl J Med. 2010 Jul 22;363(4):301-4. doi: 10.1056/NEJMp1006304. Epub 2010 Jun 15. Erratum in: N Engl J Med. 2010 Sep 9;363(11):1092. PMID: 20551152.
2. Collins F. Integrating the 4P's into Patient Care. November 2019. Colgate Oral Health Network for Professional Education and Development. https://www.colgateoralhealthnetwork.com/article/integrating-the-4ps-into-patient-care/?tab=content. Accessed 19 April 2024
3. Meyer JM, Ginsburg GS. The path to personalized medicine. Current Opinion in Chemical Biology. 2002 Aug 1;6(4):434-8.
4. Hood L, Flores M. A personal view on systems medicine and the emergence of proactive P4 medicine: predictive, preventive, personalized and participatory. N Biotechnol. 2012 Sep 15;29(6):613-24. doi: 10.1016/j.nbt.2012.03.004. Epub 2012 Mar 18. PMID: 22450380.
5. GlobalData Pharma Intelligence Center. https://www.globaldata.com/industries-we-cover/pharmaceutical/
6. Hapgood R. The potential and limitations of personalized medicine in the doctor–patient relationship. Pharmacogenomics. 2003 Nov 1;4(6):685-7.
7. Hood L, Balling R, Auffray C. Revolutionizing medicine in the 21(st) century through systems approaches. Biotechnol J. 2012;7:992-1001.
8. Murphy M, Badoux J, Zhang T. Fit for purpose biomarker development: a translational medicine perspective, Whitepaper; Worldwide Clinical Trials. July 2023.
9. Blue Cross of California. Medicare part D coverage criteria. AMPYRA (dalfampridine). January 2012. www.blueshieldca.com/sites/medicare/documents/PA_CY2012_AMPYRA_dalfampridine_MCweb.pdf. Accessed August 13, 2012.
10. Confeld, M, Murphy MF. When a lethal disease becomes chronic: the emergence of peer rose in oncology. Whitepaper; Worldwide Clinical Trials. March 2024.

References

11. Vieta A, Badia X, Sacristán JA. A systematic review of patient-reported and economic outcomes: value to stakeholders in the decision-making process in patients with type 2 diabetes mellitus. Clin Ther. 2011; 33: 1225-1245.

12. Alemayehu D, Cappelleri JC. Conceptual and analytical considerations toward the use of patient-reported outcomes in personalized medicine. American health & drug benefits. 2012 Jul;5(5):310.

13. FDA. Focus Area: Individualized Therapeutics and Precision Medicine. https://www.fda.gov/science-research/focus-areas-regulatory-science-report/focus-area-individualized-therapeutics-and-precision-medicine. Accessed. May 6, 2024.

14. FDA. Division of Translational and Precision Medicine (DTPM). https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/division-translational-and-precision-medicine-dtpm. Accessed May 5, 2024

15. FDA. IND submissions for individualized antisense oligonucleotide's drug products: administrative and procedural recommendation guidance for sponsors-investigators. January 2021. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/ind-submissions-individualized-antisense-oligonucleotide-drug-products-administrative-and-procedural. Accessed May 5, 2024.

16. Confeld M, Griner E, Gres A, Sandroni P, Kuhlman A, Murphy M. Master protocols: the opportunities and challenges of baskets and umbrellas, expanding the translational toolbox. Whitepaper; Worldwide Clinical Trials. November 2023.

17. Confeld M, Williamson J, Fishbein G, Murphy M. Leadership in oncology: the culture of improving patient outcomes. Whitepaper; Worldwide Clinical Trials. October 2023.

18. Gayet-Ageron, A., Rudaz, S. & Perneger, T. Biobank attributes associated with higher patient participation: a randomized study. Eur J Hum Genet 25, 31–36 (2017). https://doi.org/10.1038/ejhg.2016.132

19. Meregaglia M, Malandrini F, Angelini S, Ciani O. The Assessment of Patient-Reported Outcomes for the Authorisation of Medicines in Europe: A Review of European Public Assessment Reports from 2017 to 2022. Appl Health Econ Health Policy. 2023 Nov;21(6):925-935. doi: 10.1007/s40258-023-00827-3. Epub 2023 Sep 2. PMID: 37659000; PMCID: PMC10627987

20. Frost J, Okun S, Vaughan T, et al. Patient-reported outcomes as a source of evidence in off label prescribing: analysis of data from PatientsLikeMe. J Med Internet Res. 2011;13:e6.

21. Sprangers MA, Sloan JA, Barsevick A, et al. Scientific imperatives, clinical implications, and theoretical underpinnings for the investigation of the relationship between genetic variables and patient-reported quality-of-life outcomes. Qual Life Res. 2010;19:1395-1403.

22. Cella D, Chen CI, Quek RGW, Uribarren A, Reaney M, Mastey V, Collyar D, Chassany O. Patient-reported outcomes labeling for oncology drugs: Multidisciplinary perspectives on current status and future directions. Front Pharmacol. 2022 Oct 17;13:1031992. doi: 10.3389/fphar.2022.1031992. PMID: 36339622; PMCID: PMC9634749.

Worldwide Clinical Trials

About Worldwide Clinical Trials

Worldwide Clinical Trials (Worldwide) is a leading full-service global contract research organization (CRO) that works in partnership with biotechnology and pharmaceutical companies to create customized solutions that advance new medications – from discovery to reality.

Anchored in our company's scientific heritage, we are therapeutically focused on cardiovascular, metabolic, neuroscience, oncology, and rare diseases. Our deep therapeutic knowledge enables us to develop flexible plans and quickly solve problems for our customers.

For more information on Worldwide, visit www.worldwide.com or connect with us on LinkedIn.