145

PFDD SIG: How to use PROs in early phase studies and & other hot topics

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Devin Peipert
Please provide a brief biography for the Presenting author(s)
Devin Peipert is Professor of Health Outcomes Measurement at the University of Birmingham in the UK, working within the Centre for Patient Reported Outcomes Research (CPROR) and Birmingham Health Partners Centre for Regulatory Science. He is an investigator and psychometrician focusing on the methodological advancement and application of patient reported outcomes (PROs) in clinical trials and regulatory decision-making. A significant focus of his research examines new tools and methods to quantify and manage drug intolerability across multiple therapeutic areas, including oncology and solid organ transplantation. His research in this area has been funded by the US FDA and National Cancer Institute's Tolerability Consortium.

Alexandra Lauer
Please provide a brief biography for the Presenting author(s)
Alexandra Lauer is a Therapeutic Area & Methodology Statistician at Boehringer Ingelheim. In her work she focuses on Clinical Outcome Assessments (COAs) and their robust implementation throughout the drug development lifecycle to support regulatory decision making, as well as HTA value strategies. Her research interests span the fields of PROs for tolerability in support of oncology dose finding and optimization, PRO estimands, COAs for efficacy in the fields of oncology, inflammation and mental health, and the use of psychometric analyses to enhance the understanding of measurement characteristics for COAs. Alexandra is a mathematician by training.

Evgeniya Reshetnyak
Please provide a brief biography for the Presenting author(s)
Evgeniya is an Associate Director of Biostatistics at Novartis, Global Drug Development. She provides statistical support to Phase II-IV clinical trials in the Global Health Development Unit, with the focus on neglected diseases and underserved patient populations. Prior to Novartis, she was working as a statistician in academia, at Weill Cornell Medicine, and taught graduate level data science courses at Columbia University, NY, USA. Evgeniya holds PhD degree in Psychometrics from Fordham University, NY, USA. Evgeniya's research interests include analyses of PRO data in clinical trials, and application of machine learning algorithms and AI in clinical research.

Rachael Lawrance
Please provide a brief biography for the Presenting author(s)
Rachael leads a team of statisticians at Adelphi Values Patient Centered Outcomes group, (a specialist consultancy company) and is involved in many aspects of strategy, analysis and interpretation of PRO data in clinical programmes. Prior to Adelphi, Rachael was a clinical trial statistician at AstraZeneca. Rachael has particular expertise in oncology and interest in the topic of estimands, and co-chairs the PSI/EFSPI PFDD SIG and contributes to the SISAQoL-IMI consortium initiatives. Rachael was previously the Events Director on the Board for PSI, and is still involved in the PSI Events Committee.

Konstantina Skaltsa

Please provide a brief biography for the Presenting author(s)
Konstantina is a statistician by training with over 15 years of academic and industry experience in the area of for patient-reported outcomes (PROs) and clinical outcome assessment (COA) more broadly. She serves as a subject-matter expert in psychometrics and statistics for COA endpoint strategy in drug development programs, as well as teaching statistics and clinical trials in BSc and MSc programs. Konstantina's focus is on advancing the science in COA endpoint definitions (efficacy, tolerability, diary or digital), estimands and statistical methodology, including handling of missing data. Konstantina is currently co-chairing the PFDD SIG (PSI) to promote the uptake of estimands and appropriate estimators in COA endpoints.

Single topic, multi-speaker session, Workshop or Single presentation submission

A single topic, mutli-speaker session/workshop

Single topic session or workshop abstracts

Talk 1: **Implementing Patient Reported Outcomes to Capture Tolerability in Early Phase Clinical Trials**

There is growing interest in including patient-reported outcomes (PROs) in early phase clinical trials. PROs assess how a patient feels or functions and, therefore, likely improve the accuracy of symptomatic adverse event capture while including the patient's perspective in determination of treatment tolerability. To meet this interest, methodological development to implement PROs in early phase trials is advancing rapidly. In this presentation, we will review multiple key research programmes. First, we will review the results of a recent expert roundtable that included trialists, regulators, patients, and PRO researchers focused on the feasibility of developing a core outcome set of PROs for dose finding and optimisation trials. In addition, we will discuss this roundtable's findings about how PRO data can be used in dose decisions in early phase trials. Second, we will discuss the ongoing activities of the OPTIMISE-AR: Incorporating Patient-Reported Outcomes in Dose-Finding Trials - Analysis Recommendations project, which aims to determine the PRO research objectives that could be considered for use in the context of dose finding oncology trials, and to identify appropriate statistical methods and data visualisation techniques to support analysis and presentation of PRO endpoints. We will complement these project reviews with summaries of existing literature on novel dose-finding model-based and model-assisted statistical designs and adaptations of later phase trial approaches for analysing and visualising tolerability PRO data. We will conclude with recommendations for current practice and next steps in research.

Talk 2: **Project Optimus in Action: A Multistate Modeling Approach for Benefit-Risk Assessment in Oncology Dose Finding**

The importance of the patients' voice in the clinical drug development process is steadily increasing. This is further strengthened by FDA's Patient-Focused Drug Development guidance, as well as project Optimus. The latter calls for a change in the oncology dose optimization paradigm through maximization of benefit, while improving the tolerability of patients. While the call for action is appreciated in the pharmaceutical industry, uncertainty about a meaningful combination of efficacy outcomes, such as progression-free survival, and patient self-reported tolerability still prevails.

In our talk, we present an approach that utilizes multistate models to quantify the patient's journey, thereby providing a more comprehensive assessment.

The methodology integrates patient-reported tolerability assessments to distinguish between progression-free states with and without significant tolerability impairments. This approach allows for a more holistic evaluation of survival benefits in combination with patients' tolerability outcomes.

A case study involving a phase 2/3 randomized controlled trial of an investigational drug in liposarcoma patients demonstrates the practical application of this methodology. The results underscore the potential of this approach to optimize oncology dose finding and optimization processes, thereby maximizing patient benefit and improving tolerability.

Talk 3**: Missing PRO data: case-study example in sickle cell disease**

Missing data in patient-reported outcomes (PRO) is a common and almost always unavoidable issue in clinical research. Simplified assumptions regarding missingness mechanism and improper treatment of missing data in PRO may lead to biased treatment effect estimates and incorrect conclusions.

ASCQ-Me (Adult Sickle Cell Quality of Life Measurement Information System) is a PRO tool that was specifically designed to measure quality of life of patients with Sickle Cell Disease (CSD) and is typically used in research by CSD scientific community. Sickle Cell Disease (SCD) is a severe genetic red blood cells disease with early systemic involvement that can affect multiple organs. Recurrent, unpredictable vaso-occlusive pain crises (VOC) leading to hospitalizations and chronic complications are the hallmark of the disease. Despite widespread use of ASCQ-Me in SCD clinical research, little guidance is provided by the developers of the tool regarding handling missing data. In the published literature, the missing data in ASCQ-Me is handled by either complete case or multiple imputations assuming missing at random (MAR) mechanism. However, it is reasonable to assume that some proportion of missing data can be attributed to the pain crises that CSD patients commonly experience, and thus not missing at random (NMAR) mechanism is a more appropriate assumption.

We propose to apply an estimand framework and address missing data using MNAR assumptions using the data from STAND study, phase 3 placebo-controlled randomized double-blind study of two doses of Crizanlizumab 5 mg/kg and 7.5 mg/kg in Sickle Cell Disease patients aged 12 years and older, where ASCQ-Me was collected weekly for every patient over the course of their 52-week on-treatment period. Specifically, depending on the reason of missingness, we will employ retrieved dropout imputations and other methods which will then be compared with the ultimate goal of providing a much needed guidance to the CSD scientific community on the proper handling missing data in ASCQ-Me.

Talk 4: Taster of hot topics from the PFDD SIG

We will briefly summarise active topics from SIG members; including how to minimise missing & aberrant PRO data in clinical trials with risk-based monitoring approach; how structure equation modelling (SEM) approaches can be applied to clinical trial PRO endpoint analysis; and statistical challenges with diary and other digitally collected data such as sensors. Please listen and find out how to join our SIG and contribute to these and other topics.