23

Designing a seamless P1/P2a open enrollment CRM dose escalation study

Elias Laurin Meyer[1], Tom Parke[2]
[1]Berry Consultants, Vienna, Austria. [2]Berry Consultants, Abingdon, United Kingdom

Elias Laurin Meyer
Please provide a brief biography for the Presenting author(s)
Elias Laurin Meyer studied statistics at the University of Vienna, where he completed his bachelor's degree in 2016 and his master's degree in 2018. He worked at the Center for Medical Data Science at the Medical University of Vienna (head: Martin Posch) from 2016 to 2023 and completed his PhD studies in 2022 under the supervision of Franz König. His thesis “Designing exploratory platform trials” was embedded in the EU-PEARL project. After completion of the EU-PEARL project, he joined Berry Consultants, where he is currently employed as a Statistical Scientist and works mainly on the design of clinical trials and clinical trial simulation software.

Tom Parke
Please provide a brief biography for the Presenting author(s)
Tom got a first in mathematics and computer science at Bristol University so long ago that it probably doesn’t count for anything anymore. He then had a fairly conventional career in low-level software engineering (compilers, operating systems and real-time control systems) before stumbling across adaptive clinical trials. Tom had the great good fortune to project manage the implementation of the ASTIN Stroke trial for Pfizer in 1998, building a system to support a trial that used Bayesian dose response modelling, performing response adaptive randomization across 16 doses. He never looked back and has worked on supporting adaptive trials ever since, implementing trial simulators and systems to support adaptive trials. He has worked on the FACTS trial simulator since its inception and leads the software team at Berry Consultants.

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

A single presentation/poster

Single presentation or poster submission

Traditionally, phase I dose escalation designs aim to find the maximum tolerated dose (MTD), usually the highest dose whose probability to cause dose-limiting toxicities stays below a certain target toxicity level, and an adequate dosing scheme. In practice, however, focus on the MTD when selecting doses to take into registration trials often leads to exposing many trial participants to doses that either produce more toxicity without increased efficacy or severe toxicities that could both limit the options for receiving benefits or lead to premature discontinuation and missed opportunity for continued benefit. Recently, FDA launched Project Optimus with the aim of educating and innovating all stakeholders to, among other goals, move towards designing dose escalation trials that attempt to find “optimal” doses, where optimality comprises safety, tolerability and efficacy.

In this talk, we draw from our in-house experiences of designing first-in-human oncology trials to present a seamless phase 1 / phase 2a dose escalation design using open enrollment guided by the continual reassessment method (CRM) that evaluates both safety and efficacy. We introduce advanced CRM adaptations such as open enrollment, target toxicity intervals and escalation with overdose control, early stopping rules, backfilling and

frontfilling, ad-hoc rules, etc., that not only vastly improve the performance and customizability of CRM, but also help identify “optimal” doses to take forward into registration trials. Finally, we discuss how to design and simulate such trials with the aid of targeted software and share insights on how to best communicate such designs with a clinical development team.