Thursday 25 July 2024

09:00-12:30 Mini Symposium 1 (Room 1)

Beyond conventional RCTs: Exploring design options and modeling in drug development

Organizers: Marcia Rueckbeil, Els Goetghebeur, Mouna Akacha in collaboration with the ISCB Sub-Committee "Statistics in Regulatory Affairs" (SiRA)

Co-chairs: Marcia Rückbeil and Tim Friede

Beyond conventional randomised controlled trials: patient reported outcomes in single arm studies

Saskia le Cessie (Leiden University, Netherlands)

Single arm trials (SAT) can serve as alternatives to randomized control trials, for example to accelerate drug approval for new promising treatments in seriously ill patients, to study treatments for rare diseases, and in situations where randomization is not feasible or ethical. However, the lack of a randomized control group may compromise the validity of conclusions, particularly when assessing the effect of a specific treatment on Patient Reported Outcomes (PROs), such as quality of life, in a single arm study.

In this talk we will discuss several issues which arise in the design and analysis of SATs with PROs. Research questions on PROs in SATs may be descriptive or confirmatory. In both cases, the ICH-E9 estimand framework for clinical studies can help define relevant research questions. We demonstrate that different summary measures and different approaches to handle intercurrent events may give different results and conclusions, even in a descriptive setting. Specifically, addressing death should be carefully considered in advance, as patient reported outcomes after death are not defined. Furthermore, missing data are a potential source of bias in the results, as reasons for missing data may depend on the patient's medical condition. We address some new methods to deal with it.

Making statements on treatments in single arm studies is challenging as changes over time in PROs cannot be solely attributed to the treatment. Various factors such as natural changes over time (e.g., due to disease worsening), response shift and the effects of concomitant therapies and comorbidities may also contribute to observed changes.

An alternative is to compare the results of a SAT to external data. This also possesses challenges: from defining a relevant estimand for the treatment effect, to accounting for confounding and different study drop out.

The work presented here is part of the European IMI-SISAQOL project. SISAQOL-IMI is an international project, led by the European Organisation for Research and Treatment of Cancer and Boehringer Ingelheim. The aim of this four year project is to establish international standards in the analysis of patient reported outcomes and health-related quality of life data in cancer clinical trials.

1. ICH E9 (R1) addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials
2. Pe M, et al.; SISAQOL-IMI Consortium. Setting International Standards in Analyzing Patient-Reported Outcomes and Quality of Life Endpoints in Cancer Clinical Trials-Innovative Medicines Initiative (SISAQOL-IMI): stakeholder views, objectives, and procedures. Lancet Oncol. 2023 Jun;24(6):e270-e283. doi: 10.1016/S1470-2045(23)00157-2. PMID: 37269858.