M2 internship proposal:
Adaptative estimator for the net benefit of a treatment

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1 Introduction

A central question in causal inference is how to quantify the impact of a treatment or intervention on an outcome. This is often approached by estimating the average treatment effect (ATE), which represents the average difference in outcomes if everyone in a population were to receive the treatment compared to if no one were. However, in practice, interest often lies in evaluating multiple endpoints, such as benefits and risks. Traditional statistical methods face several limitations when dealing with multiple outcomes in clinical trials.

For example, one common approach is to combine all outcomes into a single composite outcome. While convenient, composite outcomes can be difficult to interpret; a treatment's poor performance on a clinically important outcome may be obscured by a strong effect on a less critical outcome. To address these challenges, methods based on prioritized outcomes have been developed [2, 3, 5]. This proposal focuses on the net benefit, a concept introduced by M. Buyse [2] and used in oncology.

The net benefit method involves defining a hierarchy of outcomes. Patients are grouped into pairs, with one patient receiving the treatment and the other receiving the control. The comparison between patients follows these principles: starting with the highest-priority outcome, the comparison moves to the next outcome only if the patients cannot be distinguished on the current one. Once a difference is identified, remaining outcomes are not considered for that pair. For each pair, it is determined whether the treated patient performed "better" or "worse" than the control patient. The net benefit is essentially the difference between the probability that a treated patient outperforms a control patient and the probability of the reverse. Typically, the net benefit is estimated using U-statistics.

2 Objectives

Recently, adaptive estimators for the Win ratio [5], a related method based on prioritized outcomes, have been introduced [4]. The goal of this internship is twofold: first, to understand and adapt the approach from [4] to the net benefit framework; and second, to develop and implement new adaptive estimators, such as targeted maximum likelihood estimators (TMLEs), for the net benefit of a treatment [1]. This projects requires developing familiarity with causal inference and semi-parametric statistics [6]

3 Opportunity for continuing to a doctoral program

A thesis grant may be considered, depending on the progress of the internship and the intern's motivation. The thesis will be co-directed by the two internship supervisors and would be funded by the project Statistical and AI based Methods for Advanced Clinical Trial CHallenges in Digital Health (SMATCH) part of the PEPR Santé numérique.

References

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[3] D. M. Finkelstein and D. A. Schoenfeld. Combining mortality and longitudinal measures in clinical trials. *Statistics in Medicine*, 18(11):1341–1354, 1999.

[4] L. Mao. On causal estimation using U-statistics. *Biometrika*, 105(1):215–220, 12 2017.

[5] S. Pocock, C. Ariti, T. Collier, and D. Wang. The win ratio: a new approach to the analysis of composite endpoints in clinical trials based on clinical priorities. *Eur Heart J.*, 33((2)):176–82, 2012.

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