

Confounding bias in pragmatic trials with a heterogeneous control arm

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1 Introduction

Clinical trials are performed under optimal conditions (artificial) for a specific population group, but their results are generalized to the average patient and used in clinical routine practice, which is not under these optimal circumstances. [9] [14] [15]. Additionally, clinical trials are inefficient, expensive, time-consuming and they often fail to meet their recruitment targets due to their strict entry criteria (restricting study population to patients that are more likely to react positively to a treatment) [5] [11] [12].

Schwartz and Lellouch (1967) recommended to make a decision for the design of a trial based on the answer that researchers want to answer ie if the question is biological then a clinical (explanatory) trial needs to be used, but if the question is about a treatment then a pragmatic trial is required. For an explanatory trial strict entry criteria may keep the population homogeneous , but for a pragmatic trial the patients should not be excluded for reasons that differ from the real clinical practice [8] [9].

Pragmatic trials are performed under the usual conditions ie on real clinical practice environment with the clinicians handling the patient [9] [11]. They do not have as strict entry criteria, they do not cost as much [10] [9] and they can be generalized to the population, when clinical trials fail to do that [6]. Pragmatic trials often compare a new treatment with the already existing treatment and not with the placebo, like in typical clinical trials [11]. Placebo is not pragmatic as it is not used in routine clinical practice [1] and there are ethical issues for not providing treatment in a placebo-controlled trial [3].

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Despite all of their advantages, pragmatic trials have additional statistical challenges compared to the clinical trials. Special consideration is required when trying to compare a new treatment with already existing multiple treatments in a pragmatic trial. Multiple treatments in the control arm create a 'type of bias' if the heterogeneity is chosen to be neglected and the results are not interpreted carefully to avoid that. In addition to this, when the decision for a treatment to be received depends on the risk of the patient, which also affects the patient's mortality then the risk of the patient is a confounder and a confounding bias is induced [4]. These two types of bias can alter the results of the data analysis that follows a pragmatic trial, mislead the analysts and lead to wrong conclusions about the true treatment effect.

2 Objective and Methods

The objective is to explore how a heterogeneous control arm can affect the true treatment estimate and to compare different methods for adjusting confounding in a pragmatic trial environment. These require simulations and the methods that will be compared are Inverse Probability Weighting, Propensity Score and Disease Risk Score Adjustment. These methods are not finalized and they are subject to change.

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