Estimand Choice and Handling of Treatment Switch in Randomized Clinical Trials

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Abstract
In placebo-controlled clinical trials patients may switch to a rescue medication or to another treatment than the initial randomized treatment due to ethical reasons if pre-defined criteria for the switch are fulfilled. As a consequence patients are withdrawn at the timepoint of their switch from the study, i.e. before the planned assessment of the primary endpoint Various estimands and imputation approaches are discussed for the specific situation of a trial where patients self-control the intake and dose of rescue medication they need with regards to their disease symptoms.

Key Words: Withdrawal, rescue medication, missing values, estimand, multiple imputation.

1. Introduction

Placebo-controlled clinical trials may allow for rescue medication up to a certain amount or frequency due to ethical reasons. Only in case of rescue medication intake more than pre-defined in the protocol, the patient will be withdrawn from the double-blind (DB) study and e.g. will roll-over to open-label treatment arm. The reliability and interpretability of results from such clinical trials depends very much on the amount of missing data after the withdrawal. Particularly, if early withdrawals would have another prognosis than the completed patients the 'missed data' after the timepoint of withdrawal would lead to substantial bias.

In future, the planning of such studies will likely be based on the estimand approach which is a structured framework to bridge trial objectives with statistical inference. An estimand reflects what is to be estimated to address the scientific question of interest posed by a trial, whereby the choice of an estimand involves: i) the population of interest, ii) the endpoint of interest, and iii) the measure of intervention effect. The measure of intervention effects takes into account the impact of so-called 'post- randomization events', like non-compliance, discontinuation of study, discontinuation of intervention, treatment switching, rescue medication or death.

An Addendum to ICH E9 (R1) is in preparation by the ICH Working Group which deals with statistical principles related to estimands and defining sensitivity analyses in clinical trials, with primary focus on confirmatory clinical trials.

In this paper the case of a placebo-controlled study will be discussed where the decision of rescue medication use to control the symptoms of the disease is in sole discretion of the patient.

2. Case Study

2.1 Study Design

The study consists of three phases: the Screening phase, the double-blind (DB) phase with the comparison of active treatment versus placebo which is assumed to be 100 days, and the open-label extension phase with the application of the active drug.
Patients are allowed to use rescue medication for symptom control (e.g. diarrhea, nausea/vomiting) throughout the study. The decision of rescue medication use (when and how much) is in sole discretion of the patient. In case rescue medication is taken e.g. 3 out of 4 weeks, or the dose is higher than allowed in more than 2 of 4 weeks, patient will be withdrawn from the DB phase and may roll-over early to the open-label extension phase. Additionally, patients may withdraw (due to other reasons than rescue medication) from the study at any time.
Daily frequency of symptoms and of rescue medication intake is recorded using an electronic daily diary. Daily mean frequency of symptoms in screening phase (serves as baseline value) and in DB phase is calculated for each patient. One of the relevant endpoints in the study is the change from baseline in the daily mean frequency of symptoms.

2.2 Missing Values and Sensitivity

How do the conclusions vary under other plausible assumptions about the behaviour of subjects after withdrawal? The aim is a targeted investigation of the robustness of the estimate in respect of a particular estimand.
The relevant investigation in this case study is the consideration of potential developments of symptom diary data of early withdrawal (EW) patients with respect to the frequency and time after their switch to open-label treatment, i.e. the potential development in the days up to 100 in the DB. Multiple imputations with varying withdrawal frequency in each treatment group and also varying timing of withdrawals were performed, but with maintaining the analysis model, the endpoint and the population. Also no intermittent missing diary data were considered. Table 1 presents three potential estimands of interest for this case study.

3. Simulation Results

Mirroring the data situation of the case study, a complete symptom dataset for all 100 subjects (50 active and 50 placebo) and for all 100 days of the DB phase were simulated, in the way that the active treatment group is superior to placebo. The effect on the treatment comparison is investigated by varying the number of EWs (10% to 30% in the treatment groups) and varying the timepoint of the EWs within the 100 days DB phase (10% to 40% missing days out of 100 days). The result of estimand 3 with missing not-at-random imputation approach is not presented, as the investigation of the case study showed only low correlation rates for rescue medication intake and symptom frequency or severity which justified the missing at-random assumption. Table 2 summarizes simulation results for estimand 1 without imputation of missing days (i.e. only the number of observed days is used as denominator) and estimand 2 with multiple imputation of missing days: p-values of t-tests are presented for treatment comparison of daily mean symptom frequency.

Table 1: Potential Estimands of Interest

	Estimand 1	Estimand 2	Estimand 3
Measure of intervention	Effect of the randomized treatment considering the observed diary days, only, until end of DB phase or EW.	Effect of the randomized treatments with all patients remained on their randomized treatments throughout the DB phase i.e. effect assuming all patients would have been observed until the scheduled end of DB phase.	Effect of the randomized treatments with all patients remained on their randomized treatments throughout the DB phase, i.e effect assuming all patients would have been observed until the scheduled end of DB phase,
Analysis variable	Change of mean daily symptom frequency from baseline. All recorded diaries are used, without imputation of missing days after EW.	Change of mean daily symptom frequency from baseline. DB phase is assumed to be 100 days. For all EWs the days after their withdrawal to day 100 are imputed.	Change of mean daily symptom frequency from baseline. DB phase is assumed to be 100 days. For all EWs the days after their withdrawal to day 100 are imputed.
Analysis model	ANCOVA model	Missing data are multiple imputed under a **missing-at-random assumption**, e.g. diary information of the patient until EW is used. For every completed data set an ANCOVA model is fitted. Overall inference by applying Ruben‘s rule on estimates of completed data sets.	Missing data will be multiple imputed under a **missing not at-random** assumption, i.e. Pattern mixture approach. For every completed data set an ANCOVA model is fitted. Overall inference by applying Ruben‘s rule on estimates of completed data sets.

Table 2: Simulation Results for Estimand 1 and Estimand 2

Complete data-set without EW p-value	% of EW Active vs placebo	% Days missing: Active vs placebo	Estimand 1: p-value	Estimand 2: p-value
0.0317	20% vs 20%	20% vs 20%	0.0400	0.0467
0.0317	20% vs 20%	20% vs 40%	0.0531	0.0474
0.0317	20% vs 20%	30% vs 10%	0.0619	0.0657
0.0317	20% vs 20%	40% vs 20%	0.1013	0.0948
0.0317	10% vs 30%	40% vs 20%	0.0441	0.0454
0.0317	10% vs 30%	40% vs 40%	0.0566	0.0669
0.0317	30% vs 10%	20% vs 20%	0.0714	0.0713

The superiority of the treatment group is sustained for up to 40% missing days in case of only 10% withdrawal rate or up to 20% missing days in 20% withdrawal rate in the treatment group. Even if the withdrawal rate or the percentage of missing days in the placebo group is 10% to 20% higher than in the active group, the superiority of active group is still given.

3. Summary

Missing data in clinical trials is a common problem. Patients may withdraw from the study due to rescue medication intake or other reasons. Several estimands of interest are proposed which consider different handling of missing values. In the case of assessing disease symptoms by daily diary data and defining the efficacy parameter as the mean daily frequency of symptoms assessed during the DB phase, the multiple imputation results do not differ significantly from the approach of using the observed days without imputation. Also, the effect of the level of missingness - in means of patient withdrawal rate and of percentage missing days – is investigated with respect to treatment comparison: the suggested approaches can cope rather well with moderate missing rates of 20% to 40%.

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