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Practical considerations for Intercurrent Events and Multiple Imputation

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ABSTRACT

Estimands in clinical trials provide the framework to estimate the treatment effect given the influence of intercurrent events (ICE). ICE occur after randomization or initial treatment and are defined in terms of how they affect study assessments or the interpretation of final results. However, ICE are not merely incidental missing data, they are defined by their relation to study treatment and the clinical question posed by the trial.

When the estimand and ICE are conceived, it is important to have both clinical and statistical input; ICE strategies other than 'treatment policy' should be justified. The strategy for addressing ICE must properly evaluate how events could be related to treatment evaluation. Practical consideration must be made for handling ICE along with other/incidental missing data. Multiple imputation process must be consistent with the ICE strategy. Additionally, clinical efforts must be made to collect 'retrieved dropouts' so that unobserved data from patients who discontinue study treatment can be properly modeled.

INTRODUCTION

While working on a variety of clinical trials, it has become clear that expectations and guidance from regulatory agencies will continue to develop. Many clinicians, programmers and statisticians are still unfamiliar with the process of determining an estimand and identifying its intercurrent events. Furthermore, there are a variety of methods to handle patients' missing or unobserved data following an intercurrent event beyond a 'treatment policy' approach. This paper will provide a starting point for identifying intercurrent events and methods of imputation in the SAS programming setting.

Multiple Imputation (MI) has become a standard method of imputing missing data, whether incidental or due to an intercurrent event. Both standard SAS Macros and open-source macros/programs – not to speak of the many R packages – provide a variety of options to impute missing data. The proper reference distribution, placebo/control arm, retrieved dropouts, or a hypothetical worst case scenario, should be discussed with sponsor clinicians with statistical input.

ESTIMANDS & INTERCURRENT EVENTS

As one of the five components of a clinical trial estimand – along with Treatment, Population, Variable and Population Level Summary - Intercurrent events (ICE) are defined as *"… events occurring after treatment initiation and affect either the interpretation or the existence of the measurements associated with the clinical question of interest… " (ICH E9, 2021)* Some common examples would be discontinuation of study treatment due to an adverse event, prohibited medications, or death. This ICH graphic provides an excellent starting point for a conversation with clinicians:

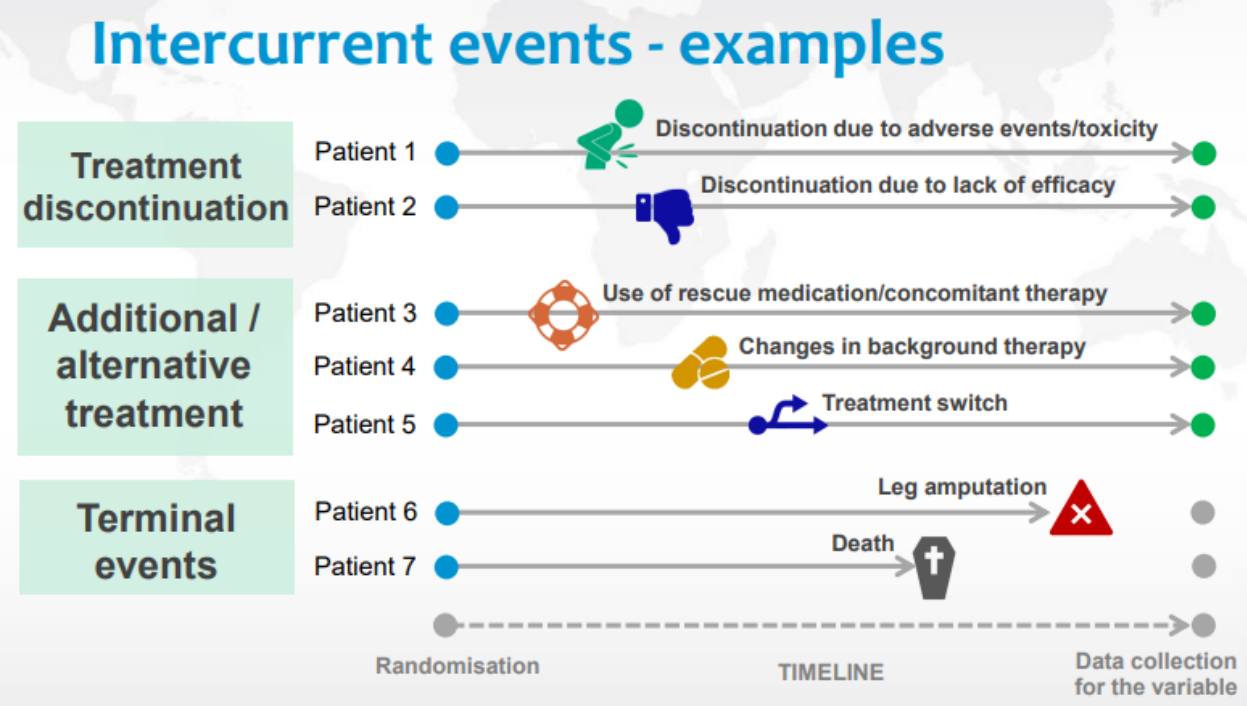

Figure 1 Intercurrent Events (ICH E9, 2021)

During protocol development, both the clinician and statistician should provide input to determine a set of ICE. ICE are selected by how they affect the patient's treatment regimen or the endpoint of interest. This is important so that ICE can be considered during database design and not in an ad-hoc fashion. This will also reduce bias in planning and implementing the analysis. ICE can be collected as part of the CRF (so monitored and cleaned in the same manner as the efficacy assessments they are relevant to) or may need to be adjudicated near the end of the trial (ideally, in a treatment-blind manner). Sponsors should make a concerted effort to collect follow-up assessments, regardless of a patient's ICE/study status.

HANDLING MISSING OR UNOBSERVED DATA DUE TO INTERCURRENT EVENTS

It is important to understand that ICE are not necessarily missing data. Indicental missing data (referred to just as 'missing data' here), for example: due to a late or missed visit assessment, withdrawal of consent or lost to follow-up, can be considered missing at random(MAR) in some contexts. In contrast 'unobserved data' will refer to data following ICE that was not collected due to that intercurrent event. The SAP should provide rules for handling missing data and test any assumptions with a sensitivity analysis.

The ITT principle is extended to the estimand's ICE when following 'treatment policy', defined as when "the occurrence of the intercurrent event is taken to be part of the treatment condition. ... Thus, participant outcomes are used regardless of whether they experienced the intercurrent event or not." (ICH E9, 2021) This (Treatment Policy) approach can be the starting point or default method for handling patients with ICE, whether this leads to unobserved data/assessments or not.

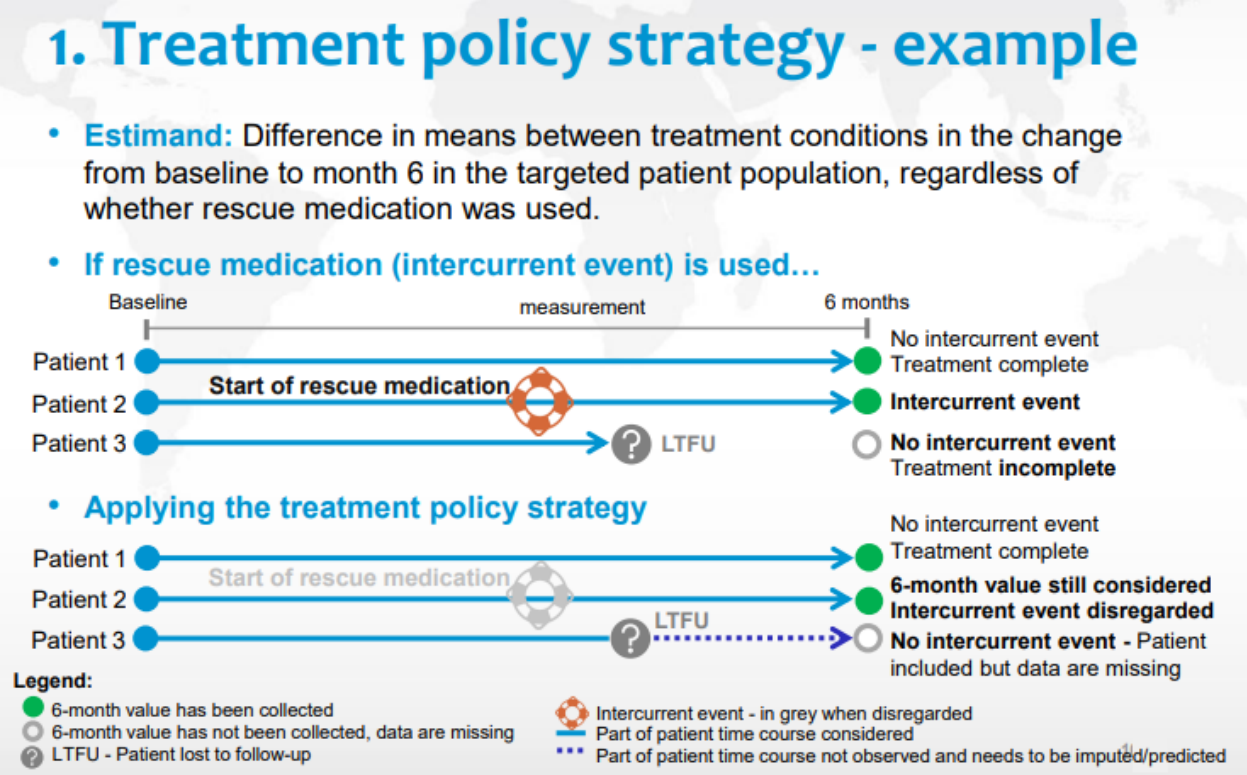

Figure 2 Treatment Policy (ICH E9, 2021)

The ICH graphic above or study specific examples of possible ICE can help clinicians understand the Estimand's assumptions. As ICE are specified, clinicians can be prompted to decide which can fall under the treatment policy (use data as observed) and which need to be imputed (none to use or data is not valid following ICE). From there, statisticians can make suggestions about the proper reference for each type of unobserved data (due to ICE).

References-based imputation distribution (Tan/Cro/Van Vogt, 2021)

> *Data are imputed following the distribution observed in a particular reference group in the trial, typically another treatment arm. … A number of different reference-based multiple imputation approaches can be constructed … J2R imputes missing data assuming participants jump to behave like those in the specified reference group (e.g. either the treatment or control arm) following their last observed time point.*

Usually, unobserved data following an ICE will be considered missing not a random (MNAR); this is when the randomized arm's full distribution would be an overly optimistic or incorrect reference for imputation models. Typically, MNAR strategies are usually thought of as using the Placebo or control arm distribution, there may be better options, such as retrieved dropouts.

Sponsors have always attempted to reduce missing data, doing so in the context of intercurrent events (ICE) can provide a proper reference for unobserved data. "Retrieved dropouts" are observed data following the specific intercurrent event of treatment discontinuation. Retrieved dropouts from each category of ICE can provide an ideal reference for unobserved data. The usefulness of this method could be limited due to the number of available 'retrieved dropouts' versus the number of missing assessment following an ICE (Wang, 2022).

In the example of a group of patients that stop active treatment halfway through a trial, some may continue to contribute to follow-up assessments. Given enough of these retrieved dropouts, it might be better to reference their available data (their collective distribution) as a basis for imputation. A control or Placebo arm could be used as a fallback reference if retrieved dropout data is inadequate.

* * *

Other components of the Estimand can dictate the ICE method. 'While on Treatment' can be relevant when the response to treatment prior to an ICE is of interest. That would be defined as part of the Treatment Condition or Variable of Interest: '… until treatment failure', '… prior to emergency/prohibited medication' or death.

An alternative option, the hypothetical method, would attempt to impute unobserved data. A punitive sample, such as the worst 5-10% of observed data or, if relevant, a worst case assessment value/score could be implemented with some clinical guidance. The composite (variable) method could assign a rank based on both the endpoint value and ICE, demoting patients with ICE behind non-ICE patients for example. However, this would also be specified in the Population Level Summary. Both of these, alternative methods, Hypothetical or Composite, would need some clinical justification.

MULTIPLE IMPUTATION

Like any model, MI specifications should remain within the bounds of the study assumptions. Covariates like baseline assessment, stratification factors, and treatment are the basic components of an MI model as they would be for ANOVA, MMRM, Logistic or PH regression. Additional factors to consider are demographics (age, sex, BMI) or assessments related to the endpoint (corelated with the endpoint or a similar measurement) could be considered. However, additional factors risk increasing the complexity of the model, even overfitting the imputation model(Chaput-Langlois 2024). The statistical analysis plan (SAP) should provide some flexibility in case of convergence issues due to larger proportions of missing endpoint assessments, too many covariates, or even a high number of repeated assessments to impute.

A patient's ICE information can be used/utilized with the MI model in several ways:

1. Covariate – a variable to indicate the ICE category (or similar set of ICE) to model patients with similar events; applicable when using a model for all several conditions or intermediate missing/unobserved.
2. To specify the reference population for MNAR imputation, either a control/placebo arm, a specific set of retrieved dropouts, or a set of worst case responders.
3. A method to separate the full set of patients, this way different models are applied separately, by patient or even specific time points.

Studies with several repeated measures have the benefit of additional data that can model the trend of patients on treatment. However, when the primary endpoint is the final assessment, that important last assessment will often be the most frequently missed. Intermediate missing can also occur. Whether this is handled as incidental missing data by the randomized arm/MAR or as MNAR (control arm or retrieved drop-out) might depend on the timing of an intercurrent event and require clinical insight. Off-treatment intermediate missing can be imputed to follow that patient's trend per later visits (such as a basic Proc MI, Markov Chain Monte Carlo (MCMC) approach); an alternative method or sensitivity analysis might impose a more specific distribution (such as placebo or control arm). MI can be setup to run an 'overall model' that would include all visits. Each repeated measure can be specified separately as well, this could be due to a large number of missing data or to more exactly specify a patient's reference (in the case treatment was discontinued between visits).

An example of a studies handling of missing data following a treatment policy approach:

1. Intermediate missing data are imputed with an MCMC approach, this defaults to MAR as patients are imputed by their own trend and that of their randomized arm
2. Incidental missing are imputed by the randomized treatment arm (MAR)
3. Intercurrent events that lead to treatment (but not study) discontinuation are imputed by Retrieved Dropouts (if adequate ratio of unobserved to retrieved data) or Placebo/control arm (MNAR)

   Note: similar ICE categories might be grouped by clinical approval.
4. Deaths are imputed by the distribution of the worst 5-10% of patients.

Note: Some consideration should be given to patients with multiple ICE, if they discontinued then died. For the purposes of imputing data for the primary endpoint, the timing of the ICE and how they affected unobserved data should be discussed between a statistician and clinician then documented in the SAP.

Note: Each of these would have to be implemented in independent steps and the datasets reassembled into the full set for analysis.

Note: Alternatively, #3 could be used as a sensitivity analysis for any unobserved or missing data. In that case. Unobserved data following an ICE would be imputed MAR as #2, such as an MMRM analysis including ICE category covariate(s). This decision could be evaluated depending on the type of events or the amount of missing data.

Possible wording for SAP: *Monotone missing data pattern happens in case of early termination of the study or intercurrent events. However, also non-monotone missing data ("intermediate missing data") may happen. In case of both types of missing data: the first step, impute non-monotone missing data to create a dataset with only monotone missing data patterns using PROC MI and Markov Chain Monte Carlo (MCMC) approach. The second step, monotone missing data are multiply imputed using PROC MI with MONOTONE statement based on the reference distribution as specified by Estimand. Patients must have an observed baseline or at least one post-baseline assessment to be imputed.*

An alternative to open-code SAS procedures, which require details written into the SAP or even sample code, would be to use established macros or suites of code such as those written by Carpenter/Rodgers/Kenward. A well known set of SAS macros, the "Five Macros", provides a comprehensive imputation based on several methods.

The number of imputations that are needed – along with other SAS options – are affected by the type of data, number of repeated measures, or the amount of missing data. A fair start is 30-50 imputations, increasing by 2 or 5 times for failed convergence. SAS provides some diagnostic methods for other options to adjust: initial burn-in iterations and min/max values for some types of assessments, or to incorporate ANCOVA residuals into an imputation model.

CONCLUSION

The objective of this paper was to describe a process to follow for establishing an estimand's intercurrent events, their handling of unobserved data, and some basic procedures for imputation. Statisticians need to be in dialogue with clinicians to propose solutions/options or temper expectations. Decisions should be made in advance of the study's completion with some fallback for more missing data than expected. Regulatory authorities can also provide important feedback, if not certain requirements, for unobserved or missing data. Also, that MI model specifics should be tailored to the endpoint. This paper attempts to provide simple options as a starting point for protocol development or SAP details. This was based on my personal experience as a statistician at Cytel Inc., where I have gained a lot of experience applying these ideas to a variety of studies, specifically phase III/pivotal trials.

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