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E9(R1) Program Practice and Its Application in Sensitivity Analysis

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ABSTRACT

In 2011, the FDA held a public consultation on the hypoglycemic drug Dapagliflozin, jointly developed by AstraZeneca and BMS, reflecting different understandings of treatment effects among sponsors and regulators. Prior to the release of ICH E9(R1), it was treated as a statistical analysis issue on missing data. ICH E9(R1) proposes a structured framework on estimands which reflects the design and analysis of a trial.

With the release of ICH E9(R1), the NMPA has decided to apply it to clinical trials in China starting in 2022. More and more industry alliances are beginning to learn and understand ICH E9(R1). Two years have passed, and many clinical trials have also been analyzed according to ICH E9(R1). Until now, we have conducted at least 10 studies in accordance with ICH E9(R1).

This article mainly focuses on how to understand and define an intercurrent event from a programming perspective, and a programming process is proposed from our experience. Next, we briefly introduce the impact of E9(R1) on sensitivity analysis. At the end, we mention some challenges that come with the implementation of E9(R1) and call on all colleagues involved in clinical trials to overcome challenges together.

INTRODUCTION

Efficacy is crucial for clinical trials. In confirmatory trials, if a trial is ineffective, it means that all the money and manpower invested by the sponsor in the early stage will be wasted. Proving effectiveness involves many factors, but it cannot be separated from the assumptions and applications of statistical principles.

In 1998, ICH released the E9 Statistical Principles for Clinical Trials, which is the "Bible" of pharmaceutical statistics in clinical trials. In 1999, China also drafted and released its biostatistics guidelines based on ICH E9, guiding the statistical analysis of clinical trials in China. We know that the core of E9 is to reduce bias and improve accuracy, and the best methods to minimize bias are randomization and blinding. However, in practical, some events that occur after randomization cannot be eliminated.

A typical case is the issue of the hypoglycemic drug Dapagliflozin mentioned in the abstract. The FDA held an expert consultation meeting to discuss whether the main analysis truly measured the therapeutic effect of the drug. In hypoglycemic drug trials, remedial treatment is inevitable, and usually statistical analysis plans provided detailed descriptions of which data is used and what analysis is conducted. However, FDA has very different views on the main statistical analysis. FDA believes that the use of LOCF to handle missing data in diabetes has limitations and prefers to impute the missing data using the values after rescue medications. And in 2010, the NRC mentioned the Estimand when reporting on the methods to handle missing data in clinical trials.

In 2019, ICH E9(R1) was officially released. It proposes a framework of estimand to strengthen dialogue among all parties involved in setting clinical trial objectives, design, implementation, analysis, and interpretation, as well as between sponsors and regulatory agencies on the clinical issues that clinical trials should address. It further confirms the causal relationship between treatment and efficacy based on E9, accurately quantifying the effectiveness of treatment, and requiring the correct handling of expected possible intercurrent events. In January 2021, the National Medical Products Administration announced that the application of ICH E9(R1) would start from January 2022.

FIVE ESTIMAND ATTRIBUTES

Firstly, let's introduce the five attributes of the estimand. The attributes below are used to construct the estimand, defining the treatment effect of interest.

Attributes	Definition	Examples
Treatment	The treatment condition of interest and, as appropriate, the alternative treatment condition to which comparison will be made (referred to as “treatment” through the remainder of this document).	"Investigational drug + remedial treatment" vs "Control drug + remedial treatment";
Population	The population of patients targeted by the clinical question. This will be represented by the entire trial population, a subgroup defined by a particular characteristic measured at baseline, or a principal stratum defined by the occurrence (or non-occurrence, depending on context) of a specific intercurrent event. Corresponds to the indications but is not equivalent to the enrolled population in the clinical trial.	Patients with severe COVID-19;
Variable	Endpoint of clinical trial, to address the clinical question. The specification of the variable might include whether the patient experiences an intercurrent event	Clinical response achieved within 15 days after randomization;
Intercurrent events	See below	See below
Population-level summary	A basis for comparison between treatment conditions.	Odds ratio of clinical response between treatment

Table 1. Five Attributes of the Estimand

DEFINE AND HANDLE INTERCURENT EVENTS IN A CLINICAL TRIAL

Due to the implementation of E9(R1), we need to first define intercurrent events in the dataset, and then we need to adopt different processing strategies for different intercurrent events. This chapter mainly explains what intercurrent events are and the strategies for handling them.

DEFINE INTERCURENT EVENTS (ICE)

Intercurrent events are events occurring after treatment initiation that affect either the interpretation or the existence of the measurements associated with the clinical question of interest

According to the definition, let's judge intercurrent events by three key points simultaneously:

Key Points	Description or Example
Occurring after treatment initiation	Received some special treatment in the past is not an ICE, while early termination of treatment due to lack of efficacy or adverse events after treatment is considered an ICE.
Affects the treatment of subjects	Treatment transfer, use of a rescue therapy

Key Points	Description or Example
Affect either the interpretation or the existence of the measurements associated with the clinical question of interest	If other prohibited drugs are taken during treatment and affect the interpretation of variables, it is considered an ICE; Long term treatment with a single missed dose or incorrect daytime medication timing is considered a violation of the protocol. If it is expected that it will not affect the interpretation of the variable, it is not considered an ICE.

Table 2. Three Key Points to Judge Intercurrent Events

Consideration of intercurrent events is required when constructing the estimand. So, what a programmer needs to do is to identify the ICEs and define them in the dataset. We need to create two types of variables in the ADSL. First type is the variable to show whether an ICE happen or not, the other one is to record the happen date, which is useful when handling the ICEs.

HANDLE INTERCURENT EVENTS WITH STRATEGIES

The following presents the processing strategies for intercurrent events in the form of a list:

Name	Description
Treatment policy strategy	The occurrence of the intercurrent event is considered irrelevant in defining the treatment effect of interest.
Hypothetical strategies	A scenario is envisaged in which the intercurrent event would not occur: the value of the variable to reflect the clinical question of interest is the value which the variable would have taken in the hypothetical scenario defined.
Composite variable strategies	An intercurrent event is considered in itself to be informative about the patient's outcome and is therefore incorporated into the definition of the variable.
While on treatment strategies	Response to treatment prior to the occurrence of the intercurrent event is of interest.
Principal stratum strategies	When the population of interest is those who potential to experience (or not experience) intercurrent events, consider using the principal stratum strategy. At this time, the clinical question of concern is to consider the principal stratum population. It is necessary to distinguish between the principal stratum and subsets (subgroups), the former based on potential non occurring or co-occurring event populations, and the latter based on already occurring intercurrent events.

Table 3. Processing Strategies for Intercurrent Events

Next, we use an example to illustrate the process of handling intercurrent events in the program.

Program Process

We use an ICH E9(R1) simulation project to illustrate the program flow for handling intercurrent events and imputing missing data.

The following is a summary table of strategies for handling target intercurrent events:

Intercurrent Events	Primary Estimand	Secondary Estimand 1	Secondary Estimand 2
Discontinuation of assigned treatment	Treatment policy strategy	Composite variable strategies	While on treatment strategies
Suspend medication	Treatment policy strategy	Treatment policy strategy	Treatment policy strategy

Intercurrent Events	Primary Estimand	Secondary Estimand 1	Secondary Estimand 2
Rescue therapy	Hypothetical strategies	Treatment policy strategy	While on treatment strategies
Background treatment changes	Treatment policy strategy	Treatment policy strategy	Treatment policy strategy
Death	Hypothetical strategies	Composite variable strategies	While on treatment strategies

Table 4. Strategies Example for Handling Target Intercurrent Events

After understanding the processing strategy, we know that for hypothetical strategies, we need to assume that no events have occurred and fill in the analysis of measurements through prediction or simulation; For the treatment policy strategy, there is no need for additional processing of the dataset, but if there are missing data, sometimes data imputation is necessary; For composite variable strategies in this example, it is necessary to define intercurrent events as treatment failure to the composite endpoint, that is, if corresponding intercurrent events occur, the measurements need to be filled in according to the results of treatment failure; For while on treatment strategies, observation data after intercurrent events will not be used.

So, what is the actual process of our dataset production? What are produced in the ADaM dataset and what are processed in TFLs?

Through extensive project experience and summaries related to E9(R1), we summarize the following processing flow:

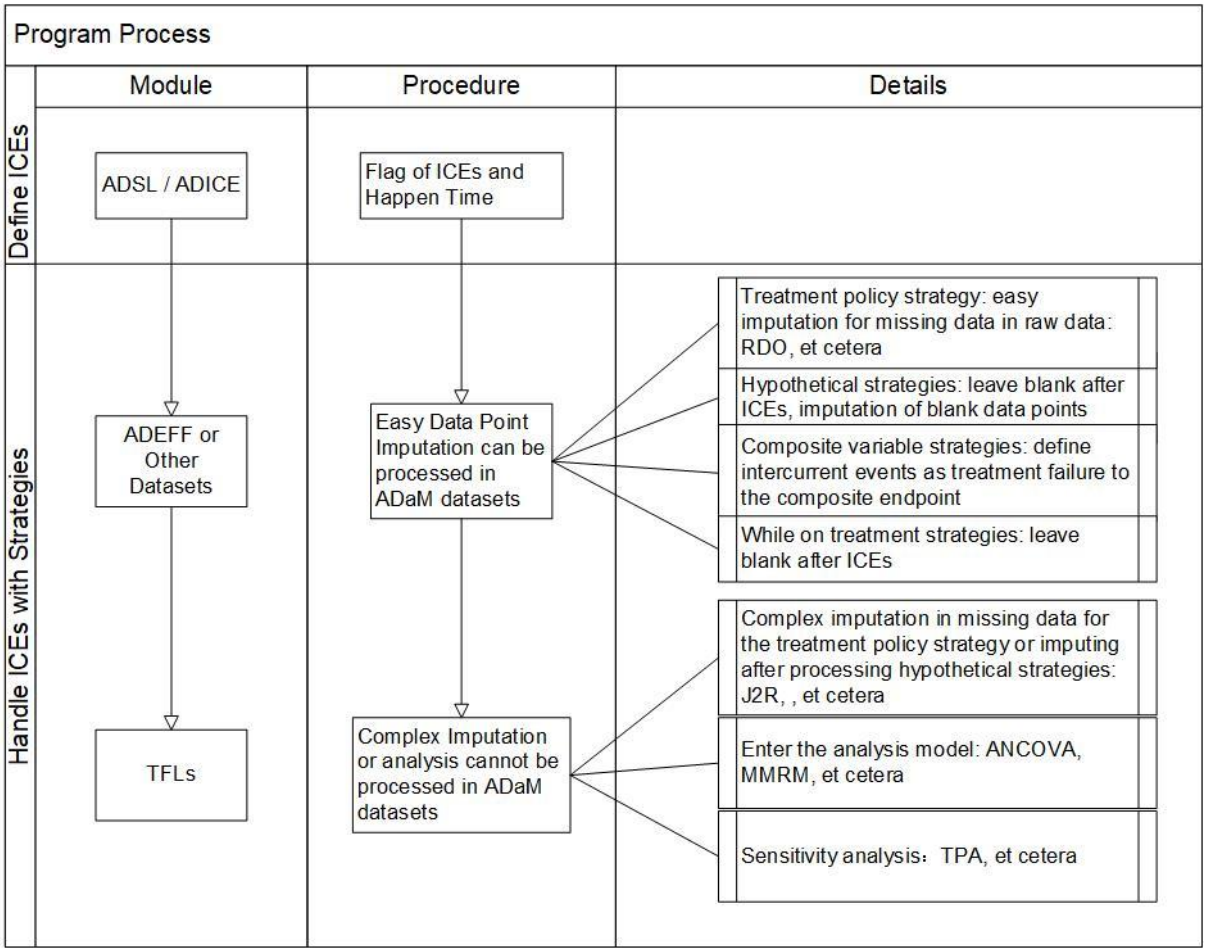

Figure 1. Program Process

The above process involves complex imputation in missing data for the treatment policy strategy or imputing after processing hypothetical strategies, such as J2R. Due to the complexity of imputation in these methods, they were not included in the dataset section for imputation.

THE IMPACT OF E9(R1) ON SENSITIVITY ANALYSIS

Firstly, we know that sensitivity analysis is an exploration of the robustness of the main analytical methods.

On the basis of further defining "sensitivity analysis", E9(R1) introduces the concept of "supplementary analysis". What is the difference between the new sensitivity analysis and the old sensitivity analysis?

Let's recall five attributes of estimand, namely "treatment", "population", " intercurrent events", "variable", and "population-level summary". New sensitivity analysis within E9(R1) is to evaluate the robustness of limitations in the data and deviations from the assumptions used in the statistical model for the main estimator. Sensitivity analysis refers to changes made only to the assumptions relied upon by the main analysis method (such as the proportional risk assumption when using the Cox proportional risk model), or analysis conducted using different methods for data defects, while targeting the same estimand (such as using RMST analysis that does not rely on the proportional risk assumption).

EXAMPLE

Previously, we often referred to sensitivity analysis as "analysis based on the Per Protocol Set (PPS)" and "treating the use of subsequent anti-tumor therapy as an event". Does this still belong to sensitivity analysis under the E9 (R1) framework?

Name	E9	E9(R1)	Comments
Analysis based on the Per Protocol Set (PPS)	Sensitivity analysis	Supplementary analysis	For analysis based on PPS we don't have a precise definition of estimand. This does not have the same estimand.
Treating the use of subsequent anti-tumor therapy as an event	Sensitivity analysis	Supplementary analysis	The management strategy for intercurrent events "treating the use of subsequent anti-tumor therapy as an event" has been changed from the original treatment policy strategy or hypothetical strategy to a composite variable strategy, which is equivalent to changing the attributes of "variable"

Table 5. Comparison between Old and New Sensitivity Analysis

The above supplementary analysis actually answers clinical questions that are different from the assumptions of our main estimation, so the strength to support the main analysis results is very limited.

CHALLENGES

During the implementation of E9(R1), there are some challenges as follows:

Challenges	Bad Result	Potential Solution
Submitted trial did not follow E9(R1) while regulatory authority requires	Revise the protocol, re-analyze the trial and even redesign database	Consider and discuss ICEs with regulatory authority when design trials
Did not design the terms associated with ICEs in CRF	Redesign database or find other ways to transfer ICEs' information	Review CRF before online by Statisticians and other related colleagues
Some ICEs cannot be confirmed until data lock	Affect the timeline of delivery or the quality of analysis results	Advance to determine ICEs and strategies

Challenges	Bad Result	Potential Solution
…		

Table 6. Challenges and Potential Solution

CONCLUSION

This paper discusses the impact of intercurrent events on programming work from the perspective of statistical programming, and summarizes a practical statistical programming process based on experience, after briefly introducing the source and history of E9(R1). Then, we give a brief introduction to the differences between the old and new "sensitivity analysis" within the framework of E9(R1), along with the introduction of the "supplementary analysis" mentioned in E9(R1). Finally, we call on all colleagues during clinical trials to work together to deal with some challenges.

Although we summarize a general statistical programming process, some parts are summarized from a practical rather than standardized perspective. We hope that everyone can propose more effective and standardized processes. In addition, with the promotion and use of E9(R1), more and more trials require programmers to implement the operation of E9(R1) at a program level. If today is your first-time hearing about E9(R1), we hope you recognize the importance and urgency of learning and mastering it to better cope with future challenges.

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