Paper DS13

Estimands: How to Make ADaM Implementation Your Friend

Jaclyn Amberg, Metronomia Clinical Research GmbH, Munich, Germany
Dennis Kusian, Metronomia Clinical Research GmbH, Munich, Germany

ABSTRACT

The concept of estimands introduced in ICH E9 (R1) [1] is more and more used in clinical trials and required by authorities. Nevertheless, at the time of first implementations of this concept, no established guidance about details of implementation in data standards, especially in ADaM, was available.

Motivated by examples from real clinical studies, we present approaches that we implemented, as well as challenges we faced, during set-up and conduct of statistical programming activities. The focus is especially on strategies to address intercurrent events (ICEs) for analysis, on data selection for different estimands in ADaM, and on the implementation of different imputation approaches.

We also show our solutions in more complex settings like multiple ICEs by subject or varying strategies for different estimands.

INTRODUCTION

Recently, we were involved in the statistical evaluation of two clinical studies where the estimand concept was to be implemented. When programming started for these studies, not much guidance was available on how the estimands could be exactly incorporated into data standards and especially into ADaM programming. Therefore, we developed several approaches for how the different analysis strategies could be incorporated.

With the publication of the draft PHUSE Whitepaper [2], more guidance became available and based on our experience from the evaluated studies, we developed the concept proposed in this paper.

The main challenges we faced during programming were the following:

- Primary and (key) secondary estimands, with a special focus on ICEs and their influence on the corresponding endpoints.
- Several supplementary estimands to investigate the influence of assumptions on the estimand attributes, especially ICEs.
- Sensitivity analyses for the different estimands.
- Hierarchical multiple imputation (MI) approaches for different ICEs and different strategies.
- MI on a daily basis had to be repeated for different estimands because of different imputation strategies for different estimands.

For the purpose of this paper, we developed an example study based on the challenges we faced during the set-up of the real clinical studies, to present how the estimand strategy was implemented.

DEFINITION OF ESTIMANDS IN EXAMPLE STUDY

The example study developed for the purpose of this paper is a randomized study comparing an active treatment to placebo.

The primary efficacy is measured via a “total score” that is available on a weekly basis (mimicking a quality of life or disease severity score that is collected via a weekly diary), where a higher total score is associated with a worse value. This total score will be analyzed by using any summary model comparing the mean scores in the active and the placebo group. In terms of intercurrent events, the relevant categories were identified as treatment non-compliance, prohibited medication intake, and discontinuation of treatment. Missing values will be treated using a multiple imputation (MI) approach assuming that these values are missing at random (MAR). Collected values impacted by intercurrent events are treated as described in more detail in the corresponding estimand.

Secondary efficacy is measured via a “total score 2” and similar analysis methods.

For this example study, one primary estimand is defined and several supplementary estimands to investigate the influence of assumptions on the estimand attributes. Additionally, a secondary estimand is defined with further supplementary estimands.

DEFINITION OF PRIMARY ESTIMAND INCLUDING SUPPLEMENTARY ESTIMANDS

The attributes of the primary estimand of the example study are summarized in Table 1.

Table 1 Definition of primary estimand

Attribute	Description
Treatment	Active versus Placebo
Population	Subjects with certain disease as described in protocol
Variable	Total Score (one value per week available)
ICEs	(1) Treatment non-compliance: A "Hypothetical Strategy with MAR assumption" is used, i.e. all values impacted by the ICE (after non-compliance until last collected value) are set to missing and imputed based on MAR assumption. (2) Prohibited medication with low expected impact: A "Treatment policy" strategy is used, i.e. all values impacted by the ICE (from start of medication intake until end of influence, including possible washout periods) are analyzed as collected. (3) Prohibited medication with high expected impact: A "Hypothetical Strategy with MAR assumption" is used, i.e. all values impacted by the ICE (from start of medication intake until end of influence, including possible washout periods) are set to missing and imputed based on MAR assumption. (4) Discontinuation of treatment (probably caused by treatment): A "Hypothetical Strategy with Missing Not at Random (MNAR) assumption" is used, i.e., all values impacted by the ICE (after discontinuation of treatment until last collected value) are set to missing and imputed by Jump to reference (J2R) following MNAR assumption. (5) Discontinuation of treatment (unlikely caused by treatment): A "Treatment policy" strategy is used, i.e., all values impacted by the ICE (after discontinuation of treatment until last collected value) are analyzed as collected.
Population level summary	Difference in mean score between active and placebo group

ICE = Intercurrent Event, MAR = Missing at Random, MNAR = Missing Not at Random, J2R = Jump to Reference (Missing Not at Random)

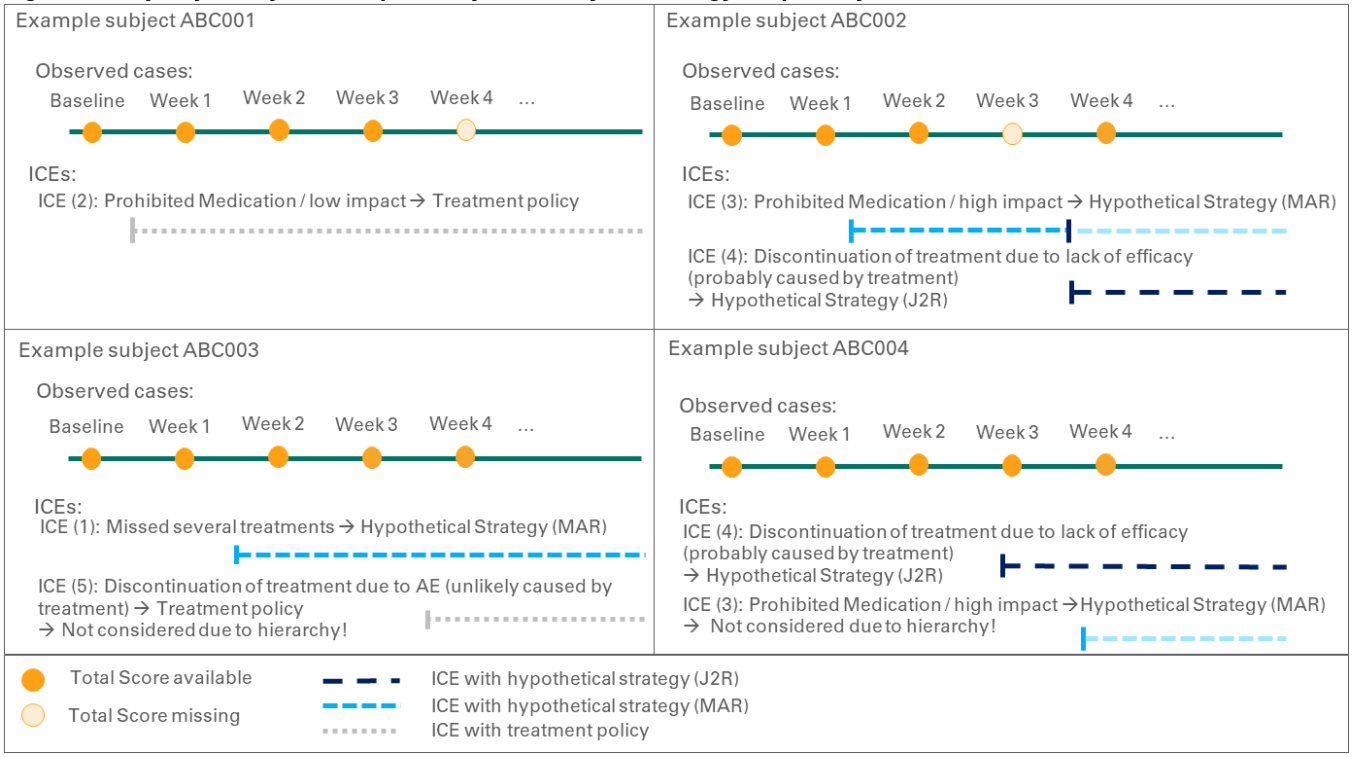
In order to decide which collected value is impacted by which ICE, the following order of ICEs is applied:

- If an ICE occurs that should be handled with a hypothetical strategy with MNAR assumption following J2R imputation (J2R-ICE), all values after the start of this ICE will be set to missing and imputed via J2R (irrespective if other ICEs occur prior or after this ICE).
- If an ICE occurs that should be handled with a hypothetical strategy with MAR assumption (MAR-ICE), all values affected by this ICE will be set to missing and imputed via MI. Exception: If a value is influenced by a J2R-ICE, the strategy changes to J2R.starting with the timepoint of the start of the J2R-ICE.
- If an ICE occurs that should be handled with a treatment policy strategy, no further adaptions will be done, as long as no ICE with hypothetical strategy occurs in parallel.

In summary, for all values the following hierarchy of strategies will be applied: **Hypothetical strategy (J2R) > Hypothetical strategy (MAR) > Treatment policy strategy**.

Example subject journeys including ICEs and their handling strategies are illustrated in Figure 1.

Figure 1 Subject journey of example study and analysis strategy for primary stand



AE = Adverse Event, ICE = Intercurrent Event, MAR = Missing at Random, J2R = Jump to Reference (Missing Not at Random)

DEFINITION OF SECONDARY ESTIMANDS INCLUDING SUPPLEMENTARY ESTIMANDS

In order to investigate the influence of certain estimand attributes further, two supplementary estimands are defined with different strategies for some of the ICEs. Additionally, a secondary estimand is defined using a second total score, but otherwise keeping the same attributes as for the primary estimand.

Table 2 Definition of supplementary estimands for the primary estimand and the secondary estimand compared to primary estimand

Attribute	Primary estimand	Supplementary estimand 1 for primary estimand	Supplementary estimand 2 for primary estimand	Secondary estimand
Treatment	Active versus Placebo			
Population	Subjects with certain disease as described in protocol			
Variable	**Total Score**			**Total Score 2**
ICEs	(1) Treatment non-compliance: Hypothetical Strategy (MAR) (2) Prohibited medication with low expected impact: Treatment policy (3) Prohibited medication with high expected impact: Hypothetical Strategy (MAR)	(1) Treatment non-compliance: Hypothetical Strategy (MAR) (2) Prohibited medication with low expected impact: **Hypothetical Strategy (MAR)** (3) Prohibited medication with high expected impact: Hypothetical Strategy (MAR	(1) Treatment non-compliance: **Treatment policy** (2) Prohibited medication with low expected impact: Treatment policy (3) Prohibited medication with high expected impact: Hypothetical Strategy (MAR)	(1) Treatment non-compliance: Hypothetical Strategy (MAR) (2) Prohibited medication with low expected impact: Treatment policy (3) Prohibited medication with high expected impact: Hypothetical Strategy (MAR)

Attribute	Primary estimand	Supplementary estimand 1 for primary estimand	Supplementary estimand 2 for primary estimand	Secondary estimand
	(4) Discontinuation of treatment (probably caused by treatment): Hypothetical Strategy (J2R) (5) Discontinuation of treatment (unlikely caused by treatment): Treatment policy	(4) Discontinuation of treatment (probably caused by treatment): Hypothetical Strategy (J2R) (5) Discontinuation of treatment (unlikely caused by treatment): Treatment policy	(4) Discontinuation of treatment (probably caused by treatment): **Hypothetical Strategy (MAR)** (5) Discontinuation of treatment (unlikely caused by treatment): Treatment policy	(4) Discontinuation of treatment (probably caused by treatment): Hypothetical Strategy (J2R) (5) Discontinuation of treatment (unlikely caused by treatment): Treatment policy
Population level summary	Difference in mean score between active and placebo group			

ICE = Intercurrent Event, MAR = Missing at Random, J2R = Jump to Reference (Missing Not at Random)
Items colored in **red** represent the differences compared to the primary estimand.

IMPLEMENTATION OF ESTIMANDS IN ADAM

For the implementation of the estimands, two parts are considered in this paper:

First, the ICEs are collected (either via programming or via manual reporting) and then classified into their types according to the estimand definition. Following this classification, the strategy for data handling is documented (ADaM dataset ADICE).

Second, the consequences of the ICEs have to be implemented in the corresponding efficacy dataset (here ADaM dataset ADEFF).

Other attributes – like the population flags to select the appropriate population for the different estimands – are not part of this paper, but should also be considered when setting up ADaM programming.

IMPLEMENTATION OF ICES IN ADAM: ADICE

Following the structure proposed in the draft PHUSE Whitepaper [2], the variables presented in Table 3 should be added to ADICE, together with further ADaM variables to represent the ICEs of the respective study appropriately.
It is recommended to define a logical numbering of the estimands upfront and then use this numbering consistently across datasets. For example, one strategy could be to use a 2-digit-number for each estimand and align the first digit with the "main estimand" (primary or secondary) and the second digit with supplementary estimands related to the main estimands.
An extract of ADICE following this approach is presented in Table 4 In this extract, only a selection of variables for the primary estimand and two supplementary estimands is shown.

Table 3 Extract of variables to be included in ADICE

Variable	Label	Notes
USUBJID	Unique Subject Identifier	
ASEQ	Analysis Sequence Number	Unique number per record, per subject, per intercurrent event
ACAT1	Analysis Category 1	Overall category for ICEs, in the example study: • "Treatment non-compliance" for ICEs of type (1) • "Prohibited medication" for ICEs of type (2) and type (3) • "Discontinuation of treatment" for ICEs of type (4) and type (5)
ACAT2	Analysis Category 2	Specific category for ICEs, in the example study: • "Treatment non-compliance with expected impact" for ICEs of type (1) • "Prohibited medication with low expected impact" for ICEs of type (2) • "Prohibited medication with high expected impact" for ICEs of type (3) • "Discontinuation of treatment (probably caused by treatment" for ICEs of type (4) • "Discontinuation of treatment (unlikely caused by treatment)" for ICEs of type (5)
ATERM	Analysis Term	Details of the ICE
ASTDT	Analysis Start Date	Start date of the ICE. • Generally, the start date should always be available. In case, that no start date is available (e.g., prior prohibited medication with unknown start), the ICE will by definition have an influence on all efficacy values.

Variable	Label	Notes
AENDT	Analysis End Date	End date of the ICE. • The end date may be empty. The ICE will then have an influence on all efficacy values collected after the start of the ICE. • In case of prohibited medications, washout periods may have to be considered after the end date of the medication intake. This should already be included in AENDT.
EST01STR	Estimand 01 handling strategy	Handling strategy for the primary estimand, in the example study: • "Treatment policy" for ICEs of type (2) and type (5) • "Hypothetical (MAR)" for ICEs of type (1) and type (3) • "Hypothetical (J2R)" for ICEs of type (4)
EST02STR	Estimand 02 handling strategy	Handling strategy for supplementary estimand 1, in the example study: • "Treatment policy" for ICEs of type (5) • "Hypothetical (MAR)" for ICEs of type (1), type (2) and type (3) • "Hypothetical (J2R)" for ICEs of type (4)
EST03STR	Estimand 03 handling strategy	Handling strategy for supplementary estimand 2, in the example study: • "Treatment policy" for ICEs of type (1), type (2) and type (5) • "Hypothetical (MAR)" for ICEs of type (3) and type (4)
…		Further supplementary estimands may be added
EST11STR	Estimand 11 handling strategy	Handling strategy for the secondary estimand, in the example study: • "Treatment policy" for ICEs of type (2) and type (5) • "Hypothetical (MAR)" for ICEs of type (1) and type (3) • "Hypothetical (J2R)" for ICEs of type (4)
…		Further secondary estimands may be added.

ICE = Intercurrent Event, MAR = Missing at Random, J2R = Jump to Reference (Missing Not at Random)

Table 4 Extract of ADICE for example study

USUBJID	ASEQ	ACAT1	ACAT2	ATERM	ASTDT	AENDT	EST01STR	EST02STR	EST03STR
ABC001	1	Prohibited medication	Prohibited medication with low expected impact	Prohibited medication xxx	2015-01-05	2015-01-30	Treatment Policy	Hypothetical (MAR)	Treatment Policy
ABC002	1	Prohibited medication	Prohibited medication with high expected impact	Prohibited medication xxx	2015-02-14	2015-03-14	Hypothetical (MAR)	Hypothetical (MAR)	Hypothetical (MAR)
ABC002	2	Discontinuation of treatment	Discontinuation of treatment (probably caused by treatment)	Discontinuation of treatment due to lack of efficacy	2015-02-28		Hypothetical (J2R)	Hypothetical (J2R)	Hypothetical (MAR)
ABC003	1	Treatment non-compliance	Treatment non-compliance with expected impact	Missed several treatments	2015-03-14		Hypothetical (MAR)	Hypothetical (MAR)	Treatment Policy
ABC003	2	Discontinuation of treatment	Discontinuation of treatment (unlikely caused by treatment)	Discontinuation of treatment due to adverse event	2015-03-28		Treatment Policy	Treatment Policy	Treatment Policy
ABC004	1	Discontinuation of treatment	Discontinuation of treatment (probably caused by treatment)	Discontinuation of treatment due to lack of efficacy	2015-04-14		Hypothetical (J2R)	Hypothetical (J2R)	Hypothetical (MAR)
ABC004	2	Prohibited medication	Prohibited medication with high expected impact	Prohibited medication xxx	2015-04-28	2015-05-14	Hypothetical (MAR)	Hypothetical (MAR)	Hypothetical (MAR)

Strategies for Primary Estimand

Strategies for Supplementary Estimands

MAR = Missing at Random, J2R = Jump to Reference (Missing Not at Random)

IMPLEMENTATION OF STRATEGIES AFTER ICES IN ADAM EFFICACY DATA: ADEFF

Following the structure proposed in the draft PHUSE Whitepaper [2], the variables presented in Table 5 are added to the efficacy dataset, together with other ADaM variables needed for the respective analysis and dataset.

An extract of ADEFF following this approach is presented in Table 6. In this extract, only a selection of variables for the primary estimand and two supplementary estimands is shown.

Table 5 Variables to be included in ADEFF

Variable	Label	Notes
USUBJID	Unique Subject Identifier	
PARAM	Parameter	Parameter of interest, in the example study: • "Total score" as the variable for the primary estimand and corresponding supplementary estimands • "Total score 2" as the variable for the secondary estimand
AVISIT	Analysis Visit	Visit of interest, in the example study: "Baseline", "Week 1", "Week 2", etc.
ADT	Analysis Date	
AVAL	Analysis Value	
DTYPE	Derivation Type	Used to document the imputation strategy for this datapoint during the occurrence of an ICE. Whenever a value is influenced by an ICE with a strategy other than "Treatment policy", a new record is generated where AVAL is either directly imputed or set to missing and imputed in a next step, depending on the complexity of the imputation strategy to be applied. The imputation strategy for this record is documented in DTYPE. In the example study: • If a record is influenced by an ICE with strategy "Hypothetical (MAR)" for any estimand, generate a new record with AVAL empty and DTYPE = "MI-MAR". • If a record is influenced by an ICE with strategy "Hypothetical (J2R)" for any estimand, generate a new record with AVAL empty and DTYPE = "J2R-MNAR". As all imputation strategies are based on MI approaches, the affected values are set to missing in ADEFF and will be imputed in a next step. No imputed values are presented in ADEFF directly.
ICESEQ01	Impacting ICE seq. Num. for Est. 01	ICE number (ASEQ from ADICE) influencing this record for estimand "01" (primary estimand), in the example study: • If a record is influenced by an ICE with strategy "Hypothetical (J2R)" for the primary estimand, generate a new record with AVAL empty and DTYPE = "J2R-MNAR" (see note for variable DTYPE) and add the corresponding ASEQ to the new record. • If a record is influenced by an ICE with strategy "Hypothetical (MAR)" for the primary estimand (and there is no ICE with strategy "Hypothetical (J2R)", see hierarchy of ICEs above), generate a new record with AVAL empty and DTYPE = "MI-MAR" (see note for variable DTYPE) and add the corresponding ASEQ to the new record. • If a record is influenced by an ICE with strategy "Treatment policy" for the primary estimand (and there is no ICE with strategy "Hypothetical (MAR)" or "Hypothetical (J2R)", see hierarchy of ICEs above), no new record needs to be generated. Add the corresponding ASEQ to the original record. In case of several ICEs with this strategy, use ASEQ from the earliest ICE.
ICESEQ02	Impacting ICE seq. Num. for Est. 02	ICE number (ASEQ from ADICE) influencing this record for estimand "02" (supplementary estimand 1). For details in the example study, see ICESEQ01.
ICESEQ03	Impacting ICE seq. Num. for Est. 03	ICE number (ASEQ from ADICE) influencing this record for estimand "03" (supplementary estimand 2). For details in the example study, see ICESEQ01.
…		Further supplementary estimands may be added

Variable	Label	Notes
ICESEQ11	Impacting ICE seq. Num. for Est. 11	ICE number (ASEQ from ADICE) influencing this record for estimand "11" (secondary estimand). For details in the example study, see ICESEQ01.
…		Further secondary estimands may be added.
EST01RFL	Estimand 01 Record-Level Flag	Flag to select appropriate records to be used in the analysis of the primary estimand. All records should be flagged that have ICESEQ01 filled, but also records that are not influenced by an ICE, but are still to be considered in the analysis of the primary estimand.
EST02RFL	Estimand 02 Record-Level Flag	Flag to select appropriate records to be used in the analysis of supplementary estimand 1. All records should be flagged that have ICESEQ02 filled, but also records that are not influenced by an ICE, but are still to be considered in the analysis of this estimand.
EST03RFL	Estimand 03 Record-Level Flag	Flag to select appropriate records to be used in the analysis of supplementary estimand 2. All records should be flagged that have ICESEQ03 filled, but also records that are not influenced by an ICE, but are still to be considered in the analysis of this estimand.
…		Further supplementary estimands may be added
EST11RFL	Estimand 11 Record-Level Flag	Flag to select appropriate records to be used in the analysis of the secondary estimand. All records should be flagged that have ICESEQ11 filled, but also records that are not influenced by an ICE, but are still to be considered in the analysis of this estimand.
…		Further secondary estimands may be added.

ICE = Intercurrent Event, MAR = Missing at Random, J2R = Jump to Reference

Table 6 Extract of ADEFF for example study: example subject ABC001

USUBJID	PARAM	AVISIT	ADT	AVAL	DTYPE	ICESEQ01	ICESEQ02	ICESEQ03	EST01RFL	EST02RFL	EST03RFL
ABC001	Total Score	Baseline	2015-01-01	5					Y	Y	Y
ABC001	Total Score	Week 1	2015-01-08	9		1		1	Y		Y
ABC001	Total Score	Week 1	2015-01-08	.	MI-MAR		1			Y	
ABC001	Total Score	Week 2	2015-01-15	3		1		1	Y		Y
ABC001	Total Score	Week 2	2015-01-15	.	MI-MAR		1			Y	
ABC001	Total Score	Week 3	2015-01-22	12		1		1	Y		Y
ABC001	Total Score	Week 3	2015-01-22	.	MI-MAR		1			Y	
ABC001	Total Score	Week 4	2015-01-29	.		1		1	Y		Y
ABC001	Total Score	Week 4	2015-01-29	.	MI-MAR		1			Y	

ICEs affecting Primary Estimand

ICEs affecting Supplementary Estimands

Records used for analysis of Primary Estimand

Records used for analysis of Supplementary Estimands

ICE = Intercurrent Event, MI-MAR = Imputation via Multiple Imputation (MI) following Missing at Random (MAR) assumption

SELECTION OF DATA FOR RESPECTIVE ANALYSIS

For the selection of data for the analysis of the respective estimands, the record-level flags are used.

In detail, for the selection of data for the analysis of the primary estimand, all records with EST01RFL = "Y" are selected. In the next step, missing values (either missing due to originally missing data or due to ICEs) are imputed following the pre-specified strategies. In the example study, MI approaches were specified, therefore, the imputation is not performed in the corresponding ADaM dataset (here: ADEFF) directly. Instead, a record with an empty AVAL is generated and missing data is imputed in a next step multiple times for each estimand and stored as "Analysis Dataset". The MI-dataset for the primary estimand is named ADEFFM01 in the example (following the same numeric logic as for the flags).

The record selection for example subject ABC001 for the primary estimand is presented in Table 7 and for supplementary estimand 1 in Table 8. The value at Week 4 is already missing in the raw data and thus assumed to be missing at random. This value will be imputed via MI as this is planned as the standard imputation strategy for all missing values following MAR. For the primary estimand, all values collected from Week 1, Week 2, Week 3 and Week 4 are influenced by an ICE (ICE number 1) with strategy "Treatment policy", therefore, the original records in ADEFF are selected for analysis. For supplementary estimand 1, a "Hypothetical Strategy (MAR)" is applied for this ICE and therefore, all records are duplicated with a missing value and DTYPE is set to "MI-MAR". All missing values for these two estimands are assumed to follow the MAR assumption and are imputed by using the same MI method in this example. A more complex example for the primary estimand is presented in **Error! Reference source not found.** for subject ABC002 where the missing values are assumed to follow both, the MAR and the MNAR assumption, and therefore, missing values need to be imputed in several steps.

Table 7 Selection of data relevant for analysis of primary estimand: example subject ABC001

USUBJID	PARAM	AVISIT	ADT	AVAL	DTYPE	ICESEQ01	ICESEQ02	ICESEQ03	EST01RFL	EST02RFL	EST03RFL
ABC001	Total Score	Baseline	2015-01-01	5					Y	Y	Y
ABC001	Total Score	Week 1	2015-01-08	9		1		1	Y		Y
ABC001	Total Score	Week 1	2015-01-08	.	MI-MAR		1			Y	
ABC001	Total Score	Week 2	2015-01-15	3		1		1	Y		Y
ABC001	Total Score	Week 2	2015-01-15	.	MI-MAR		1			Y	
ABC001	Total Score	Week 3	2015-01-22	12		1		1	Y		Y
ABC001	Total Score	Week 3	2015-01-22	.	MI-MAR		1			Y	
ABC001	Total Score	Week 4	2015-01-29	.		1		1	Y		Y
ABC001	Total Score	Week 4	2015-01-29	.	MI-MAR		1			Y	

Missing values imputed via standard imputation strategy of the study (MI)

ICEs affecting Primary Estimand

Records used for analysis of Primary Estimand

ICE = Intercurrent Event, MI = Multiple Imputation, MI-MAR = Imputation via Multiple Imputation (MI) following Missing at Random (MAR) assumption

Rows shaded in light grey are not selected for the respective estimand.

Table 8 Selection of data relevant for analysis of supplementary estimand 1: example subject ABC001

USUBJID	PARAM	AVISIT	ADT	AVAL	DTYPE	ICESEQ01	ICESEQ02	ICESEQ03	EST01RFL	EST02RFL	EST03RFL
ABC001	Total Score	Baseline	2015-01-01	5					Y	Y	Y
ABC001	Total Score	Week 1	2015-01-08	9		1		1	Y		Y
ABC001	Total Score	Week 1	2015-01-08	.	MI-MAR		1			Y	
ABC001	Total Score	Week 2	2015-01-15	3		1		1	Y		Y
ABC001	Total Score	Week 2	2015-01-15	.	MI-MAR		1			Y	
ABC001	Total Score	Week 3	2015-01-22	12		1		1	Y		Y
ABC001	Total Score	Week 3	2015-01-22	.	MI-MAR		1			Y	
ABC001	Total Score	Week 4	2015-01-29	.		1		1	Y		Y
ABC001	Total Score	Week 4	2015-01-29	.	MI-MAR		1			Y	

Missing values imputed via MI

ICEs affecting Supplementary Estimand 1

Records used for analysis of Supplementary Estimand 1

ICE = Intercurrent Event, MI = Multiple Imputation, MI-MAR = Imputation via Multiple Imputation (MI) following Missing at Random (MAR) assumption

Rows shaded in light grey are not selected for the respective estimand.

Table 9 Selection of data relevant for analysis of primary estimand: example subject ABC002

USUBJID	PARAM	AVISIT	ADT	AVAL	DTYPE	ICESEQ01	ICESEQ02	ICESEQ03	EST01RFL	EST02RFL	EST03RFL
ABC002	Total Score	Baseline	2015-02-01	9					Y	Y	Y
ABC002	Total Score	Week 1	2015-02-08	9					Y	Y	Y
ABC002	Total Score	Week 2	2015-02-15	8							
ABC002	Total Score	Week 2	2015-02-15	.	MI-MAR	1	1	1	Y	Y	Y
ABC002	Total Score	Week 3	2015-02-22	.							
ABC002	Total Score	Week 3	2015-02-22	.	MI-MAR	1	1	1	Y	Y	Y
ABC002	Total Score	Week 4	2015-03-01	7							
ABC002	Total Score	Week 4	2015-03-01	.	MI-MAR			1			Y
ABC002	Total Score	Week 4	2015-03-01	.	J2R-MNAR	2	2		Y	Y	

Missing values imputed via MI

Missing values imputed via J2R

ICEs affecting Primary Estimand

Records used for analysis of Primary Estimand

ICE = Intercurrent Event, MI-MAR = Imputation via Multiple Imputation (MI) following Missing at Random (MAR) assumption, J2R-MNAR = Jump to Reference (J2R) following Missing Not at Random (MNAR) assumption

Rows shaded in light grey are not selected for the respective estimand.

Note: The records selected for the primary estimand in this example are the same records to be selected for supplementary estimand 1.

IMPUTATION OF VALUES IN DIFFERENT SETTINGS

In case of missing data, imputation strategies should be defined for the statistical analysis. Additionally, different strategies may be needed for data impacted by ICEs, depending on the assumptions on the influence of the respective ICEs. To implement these imputation strategies, several considerations should be made:

- Is there a single assumption about missing data in the dataset, i.e. are all values considered to be missing at random, or are all values missing because of a reason (missing not at random)?
  If this is the case, the imputation can be done in one step, in case of single imputation, this can be done directly in ADaM, in case of MI, this could be done via one MI step.
- Are several assumptions about missing data to be taken into consideration, i.e. is there a need to perform several imputation steps?
  If this is the case, one needs to check if any hierarchy of the methods needs to implemented. This is especially important if already imputed values are also taken into consideration for the imputation of other values. This is the approach used for the example study.

IMPLEMENTATION OF HIERARCHICAL IMPUTATION APPROACH

For the example study, some values are considered as MAR due to an ICE or due to missing collected values, other values are considered to be MNAR and planned to be imputed via a J2R approach.

To implement this approach for a single estimand, in a first step an MI with *m* imputations is performed for all missing values. The resulting dataset contains all data *m* times with missing values imputed separately for each of the *m* imputations. In a second step, the values that are considered to be MNAR will be set to missing and imputed again via a single J2R imputation algorithm. Thus, the values imputed in the first MI step are also used in the single J2R steps resulting in *m* different sets of records. These datasets are then used in the statistical model and the estimates are combined into one single estimate of the treatment effect. The data flow for this strategy is presented in Figure 2 for different estimands.

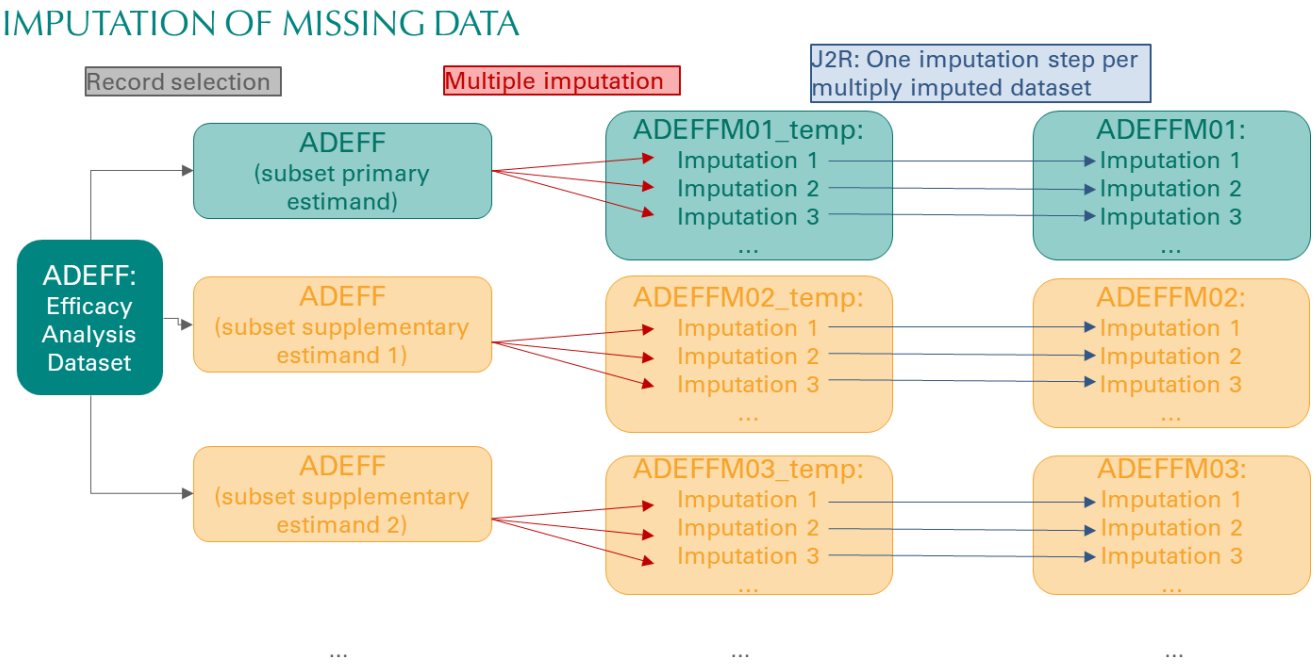


Figure 2 Data Flow for implementation of imputation

J2R = Jump to Reference

CONCLUSION

The definition and analysis of estimands has become a key concept in clinical studies and therefore the implementation of this concept in data standards is an important part of the statistical analysis. To be able to implement this appropriately, it is important to plan ADaM programming, including variables related to estimands, carefully in advance. Even though this is a complex topic, a clear strategy facilitates further analyses and enables an easier review of data.

This paper intends to give some guidance on how several estimands in a study (primary estimand, secondary estimands and corresponding supplementary estimands) could be implemented in ADaM datasets and how different strategies for intercurrent events can be handled. Using this approach, all persons involved in the programming and the review of clinical studies can benefit from a clear structure following standardized naming conventions.

One major learning we had during the implementation is the importance of a dataset containing all ICEs and corresponding strategies (ADICE). Even though the set-up of this dataset can be difficult and complex because it can be based on different

SDTM sources as well as external data, it makes sense to invest substantial effort to construct this dataset properly. ADICE ultimately becomes the basis for the estimand analysis and is therefore as important as the analysis itself. The programming of the respective efficacy dataset will become easier as all relevant ICE information is available in one dataset.

A second learning is the importance of a clear naming and numbering of estimands, so that variables across several datasets can be clearly identified to belong to a specific estimand. This makes it easier to understand the dataset structure for anyone who is not familiar with the single analyses, and also simplifies programming.

We are convinced that using a clear structure and a thoughtful planning of implementation is the key of a successful statistical analysis.

REFERENCES

[1] ICH E9(R1) Addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). Updated 20-Nov-2019. https://database.ich.org/sites/default/files/E9-R1_Step4_Guideline_2019_1203.pdf

[2] Implementation of ICH E9(R1) Estimands Framework using Data Standards. Public Review Draft. Updated 15-Nov-2023 https://phuse.s3.eu-central-1.amazonaws.com/Deliverables/Under+Review/Implementation+of+Estimands+Using+Data+Standards+-+White+Paper.pdf

ACKNOWLEDGMENTS

The authors would like to thank all colleagues from Metronomia Clinical Research GmbH that were involved in the implementation of the estimand concept as well as in the review of this paper for their support and their valuable contributions on the topic

RECOMMENDED READING

[1] ICH E9(R1) Estimands and Sensitivity Analysis in Clinical Trials - Training Module 1: Summary. Updated Dec 2021. https://database.ich.org/sites/default/files/E9(R1) Training Material - PDF_0.pdf

CONTACT INFORMATION

Contact the author at:
Author Name: Jaclyn Amberg and Dennis Kusian
Company: Metronomia Clinical Research GmbH
Address: Paul-Gerhardt-Allee 42,81245 München, Germany
Work Phone: +49 89 829265229 and +49 89 829265243
Email: jamberg@metronomia.net and dkusian@metronomia.net
Website: www.metronomia.net