Paper PP17

Bridging the Gap: Translating Intercurrent Events into Analysis - ready ADaM dataset

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ABSTRACT

With the implementation of the ICH E9 (R1) Estimand Framework, handling intercurrent events (ICEs) has become a critical part of clinical trials analysis. Events like treatment discontinuation, use of rescue medication or death can alter the interpretation of treatment effects if not properly accounted for. Statistical programmers are at the core for ensuring estimand-aligned, robust analysis ready-ADaM datasets. This paper presents a practical guide to identifying, deriving and mapping ICEs using a custom ADICE dataset. Key variables such as ESTzzSTR, ADECOD, ICESEQzz are highlighted, along with five strategy types - Treatment Policy, Hypothetical, While-on-Treatment, Composite, and Principal stratum Through mock data, a few possible mock TFLs and a dataset flowchart will be presented to demonstrate how programmers can enable estimand-alignment, transparency, and regulatory compliance.

INTRODUCTION

An estimand is a precise description of the treatment effect reflecting the clinical question posed by a given clinical trial objective. Adoption of the estimand framework can enhance the quality and interpretability of trial data, making it a valuable tool for clinical research. The estimand framework can be used widely among different therapeutic areas, different types of trials, different trial objectives, and handling of some special concomitant events (i.e. change of treatment, COVID-19 pandemic-related events, etc.) Estimand related details are generally pre-specified in protocol and effectively captured during CRF design and study conduct. More details about estimand also tends to be specified in Statistical Analysis Plan (SAP), like section of study estimand detailing on primary estimand and/or supplementary estimand for primary endpoint, Secondary estimand for secondary endpoint etc. with focus on intercurrent events and corresponding data handling strategies, and its implementation in different kind of analyses like sensitivity analysis, supplementary analysis etc. In this paper, with the example case study, focus is on Composite and Hypothetical strategies and effects of such ICE in analysis and outcome.

From programming perspective, it is essential to understand first Intercurrent Events (ICE) defined for the study and corresponding strategies for addressing ICEs mentioned in the SAP/TFL Shells and in case if multiple intercurrent events takes place for the same patient, understanding which strategy is considered as priority plus it is crucial to understand the differences among the strategies and potential impact on the datapoints that need analyses. Once these concepts are clear, create the ADaM datasets, integrate ICE in ADaM according to the analysis requirements and apply the processed data points/parameters in the specific TFL analyses.

ESTIMAND FRAMEWORK:

The ICH E9 (R1) also mentions five attributes about estimand to implement in analysis as detailed below:

Attribute	Description
Treatment	Treatment condition of interest, and treatment to be compared. For eg, A new therapy administrated vs. subcutaneous injection every two weeks.
Population	The group of patients targeted for inference For eg, Target population between a specific age range between 18-60, sex group Male with underlying condition.
Variable	The outcome or endpoint being measured For eg, A binary response/non-response at week x or time to progression of a disease.
Intercurrent Events	Events occurring after treatment initiation that affect interpretation. For eg, Treatment discontinuation due to lack of efficacy or due to any other reason apart from Lack of efficacy.

Summary Measure	The statistical method used to quantify the treatment effect. For eg, for a binary variable/endpoint - Difference in LS means using the analysis of covariance with 90% confidence intervals (CIs).

INTER CURRENT EVENTS:

Intercurrent events are events that occur **after treatment starts** and affect either the interpretation or the existence of the measurements associated with the clinical question of interest by **Preventing** the observation of the outcome, **Changing** the interpretation of the outcome, **Impacting** the relevance of the treatment effect. Example of such ICEs are Treatment discontinuation due to Safety or lack of efficacy, Use of rescue medication, Death before outcome measurement, Switching treatments.

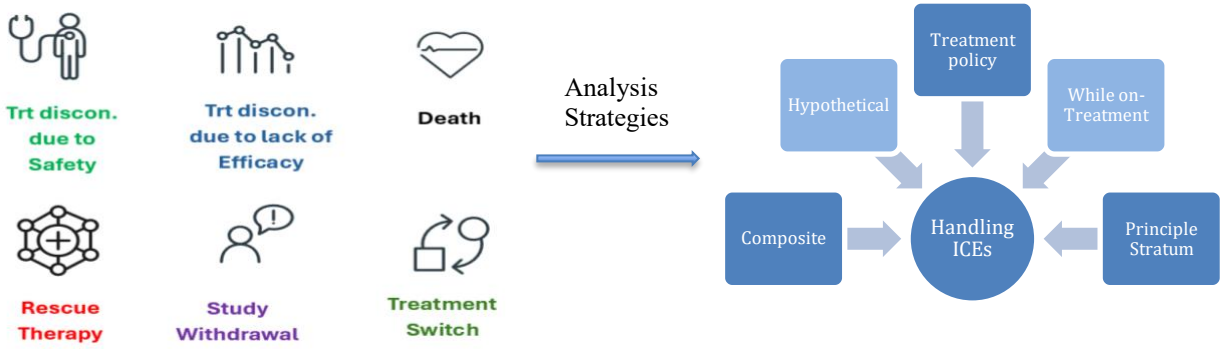

Figure 1. Common Intercurrent Events and ICE Handling Strategies.

SPECIFICS OF ICE HANDLING STRATEGIES:

Composite variable Strategies	• The ICE is considered as a part of the outcome and is incorporated into the definition of the endpoint. For eg. Early permanent treatment discontinuation due to lack of efficacy, Rescue medication usage..
Hypothetical Strategies	• Treatment Effects are estimated in the hypothetical situation where the relevent ICE would not have taken place. • For eg, Early permanent treatment discontinuations for any reason other than lack of efficacy
Treatment Policy Strategies	• ICEs are deemed to be irrelevant when estimating the treatment effect of interest. • For eg, lack of compliance or deviations from the protocol
Principal Stratum Strategies	• Treatment effects are estimated in a group of subjects for whom a potential ICE may not occur. • For e.g. Patients who would develop ADAs (Anti-Drug Antibody) if treated with the investigational biologic treatment for studies having Estimand to understand how immunogenicity impacts efficacy.
While on Treatment Strategies	• The response to treatment prior to the occurance of the ICE is of interest. • For eg, the last measurement before death(or other ICEs) or at a predefined timepoint, whichever comes first.

Figure 2. Definition of ICE handling Strategies.

EXAMPLE CASE 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 improvement 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 score is associated with an improvement value. This total Improvement score will be analyzed by using specific 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, Rescue 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 below.

DEFINITION OF PRIMARY ESTIMAND

The primary estimand for the primary endpoint is described according to the following attributes:

Table.1 Defining Primary Estimand as per Example case study.

Attributes	Description
Treatment	Active versus placebo.
Population	Subjects with certain disease as described in protocol
Variable	Total Improvement Score at Week 28.
Handling of intercurrent events	1) Early permanent treatment discontinuation due to lack of efficacy from Week 4 onwards up to and including Week 28 **(Composite variable strategy)** 2) intake of rescue medication from Week 4 onwards up to and including Week 28 **(Composite variable strategy)** 3) confirmed deterioration from Week 4 onwards up to and including Week 28 according to the definition in Protocol **(Composite variable strategy).** 4) Early permanent treatment discontinuations before Week 4 or for any reason other than lack of efficacy are handled as if these events did not happen (**Hypothetical strategy**). 5) For all other intercurrent events such as lack of compliance or deviations from the protocol - these events are ignored (**Treatment policy strategy**).
Population level summary	Difference in mean score between active and placebo group

IMPLEMENTATION OF ICE IN ADAM STRUCTURE – ADICE:

The estimand framework is explained in the protocol and SAP, therefore impacting most of the related statistical analyses. This scope of application will also reflect on how it can be implemented in the ADaM datasets supporting these analyses. The new requirements that are supported by the ADaM estimands implementation framework are:

• ADICE creation - capturing Intercurrent Events: it provides ways to organize, identify, and document intercurrent events, their relationship with each estimand and the related handling strategy.

• Adding Relationship variables in Other ADaM datasets provides ways to document analysis datapoints affected by intercurrent events which supports statistical analyses related to estimands.

Following the structure proposed in the draft PHUSE Whitepaper [2] , the variables presented in Table 2 should be added to ADICE, together with further ADaM variables to represent the ICEs of the respective study appropriately.

Table.2 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 (5) • "Prohibited/Rescue medication" for ICEs of type (2) and type (3) • "Discontinuation of treatment" for ICEs of type (1) and type (4)
ACATx	Analysis Category x	It could be defined like ACAT1 if you have more estimands defined in your study.
ATERM	Analysis Term	Details of the ICE
ADECODy	Analysis Dictionary Derived Term {y}	Coded version of the intercurrent event, at lower level of granularity needed according to intercurrent event definition.
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.
AENDT	Analysis End Date	End date of the ICE. • The end date may be empty. 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.
AOCCFL	Analysis Occurrence Flag	Record the 1st occurrence of intercurrent event within subject when subject experience multiple ICEs.
EST01STR	Estimand 01 handling strategy	Handling strategy for the primary estimand, in the example study: • "Treatment policy" for ICEs of type (5) • "Hypothetical (MAR)" for ICEs of type (4) • "Composite variable strategy" for ICEs of type(1,2,3)
ESTzzSTR	Estimand zz handling strategy	Could be defined similar to EST01STR if you have supplementary estimands for Primary endpoint or secondary/supplementary estimands for secondary endpoints

Table.3 ADICE dataset from the Example Case study.

Row	USUBJID	ASEQ	SRCDOM	SRCSEQ	ASTDT	ATERM	ADECOD1	ACAT1	EST01STR	AOCCFL
1	ABC001001	1	DS	6	2025-04-30	ADVERSE EVENT	Treatment discontinuation due to any reason other than lack of efficacy	Treatment discontinuation	Hypothetical Strategy	Y
2	ABC001002	1	ADCM	11	2024-10-23	METHYLPREDNISONE	Intake of rescue medication from Week 4 onwards up to and including Week 28	Intake of rescue medication	Composite variable strategy	Y
3	ABC001003	1	ADRS	1	2024-11-27		Confirmed deterioration with protocol defined conditions	Confirmed deterioration	Composite variable strategy	Y
4	ABC001004	1	DS	5	2025-04-25	ELEVETED LEVEL OF ALT	Treatment discontinuation due to any reason other than lack of efficacy	Treatment discontinuation	Hypothetical Strategy	Y
5	ABC001005	2	ADRS	16	2023-11-21		Confirmed deterioration with protocol defined conditions	Confirmed deterioration	Composite variable strategy	Y
6	ABC001005	1	DS	4	2024-04-14	LACK OF EFFICACY	Treatment discontinuation due to lack of efficacy	Treatment discontinuation	Composite variable strategy	

EFFECTS OF ICE IN OTHER ADAMS:

The new estimands implementation variables can be classified in 3 categories based on purpose:

1) Variable to document if a subject is relevant for an estimand (Estimands populations flags). If required, this would be added in ADSL and then repeated as a common variable in other ADaMs like ICEzzFL.
2) Variables to document intercurrent events and their relationship with estimands which would be captured in ADICE as detailed in Table 2.
3) Variables to document datapoints (Parameters) affected by intercurrent events and its impact on estimation (Estimand analysis set record flag). For example change in handling multiple imputation for missing values, the subjects who has experienced ICEs, their imputed result could get impacted depending on Composite or hypothetical strategies as described in Population level summary part of Table which is defining Estimand in SAP, For this Example case study the effects of ICE were seen on ADEFF and imputed ADEFFMI dataset which is explained below.

TABLE.4 ADDITION OF ICE RELATED VARABLES – ADEFF/ADEFFMI FROM EXAMPLE CASE STUDY:

Variable	Label	Description
USUBJID	Unique Subject Identifier	
PARAM	Parameter	Parameter of interest, in the example case study: "Total Improvement score" as the variable for the primary estimand and corresponding supplementary estimands
DTYPE	Derivation Type	To document the imputation strategy for this datapoint/parameter of interest during the occurrence of an ICE. In case where 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 case study: • If a record is influenced by an ICE with strategy "Composite variable (MAR)" for any estimand, generate a new record with AVAL set to baseline-screening value and DTYPE = "COMPOSITE-MI". • If a record is influenced by an ICE with strategy "Hypothetical" for any estimand, generate a new record with AVAL set to 0 and DTYPE = "H-MI". 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 but would be detailed in the ADEFFMI.
ICESEQ01	Impacting ICE seq. Num. for Est. 01	ICE number (ASEQ from ADICE) influencing this record for estimand "01" (primary estimand).) For Example case study: If a record is influenced by an ICE with strategy "Composite variable (MAR)" for the primary estimand (and there is no ICE with strategy "Hypothetical", generate a new record with AVAL set to baseline-screening value and DTYPE = "COMPOSITE-MI" (see description for variable DTYPE) and add the corresponding ASEQ to the new record.
ICESEQzz	Impacting ICE seq. Num. for Est. zz	Similar to ICESEQ01 if you have more than one Estimand strategy followed in the study.
EST01RFL	Estimand 01 Record-Level Flag	Flag to select the specific 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.
ESTzzRFL	Estimand zz Record-Level Flag	Similar to EST01RFL if you have more than one Estimand strategy followed in the study.

TABLE 5. SNIPBIT OF ADEFF/ADEFFMI FROM EXAMPLE CASE STUDY.

USUBJID	AVISIT	PARAM	AVAL	ICESEQ 01	EST01RFL	DTYPE	EST01STR	ANL01FL
ABC001003	Baseline	Total Improvement Score	17,50	1	Y			

ABC001003	Day 29 (Week 4)	Total Improvement Score	5,00	1	Y			
ABC001003	Day 57 (Week 8)	Total Improvement Score	7,50	1	Y			
ABC001003	Baseline	Total Improvement Score	17,50					
ABC001003	Day 29 (Week 4)	Total Improvement Score	5,00					
ABC001003	Day 57 (Week 8)	Total Improvement Score	7,50					
ABC001003	Day 85 (Week 12)	Total Improvement Score	17,50			COMPOSITE-MI	Composite variable stratergy	Y
ABC001003	Day 85 (Week 12)	Total Improvement Score	0,00			MI	Composite variable stratergy	
…	continues till Week 28	…	…	…	…	…	…	…

Here, ADEFF captures the calculated scores without any imputation being done but with additional Variables like ICESEQ01 and EST01RFL. ADEFFMI which is imputed dataset from ADEFF highlighted in above Table 5 with blue Text will have the imputed values as a result of Patient having experienced an ICE, In this example study we have different strategies to follow for Composite variable strategy for intercurrent event one example which can be observed here with COMPOSITE-MI dtype which basically gets the imputed record the value of base as per statistical summary details and ANL01FL will be used to select records for the Outputs.

TFLS SHOWING EFFECTS OF ICE FROM EXAMPLE CASE STUDY

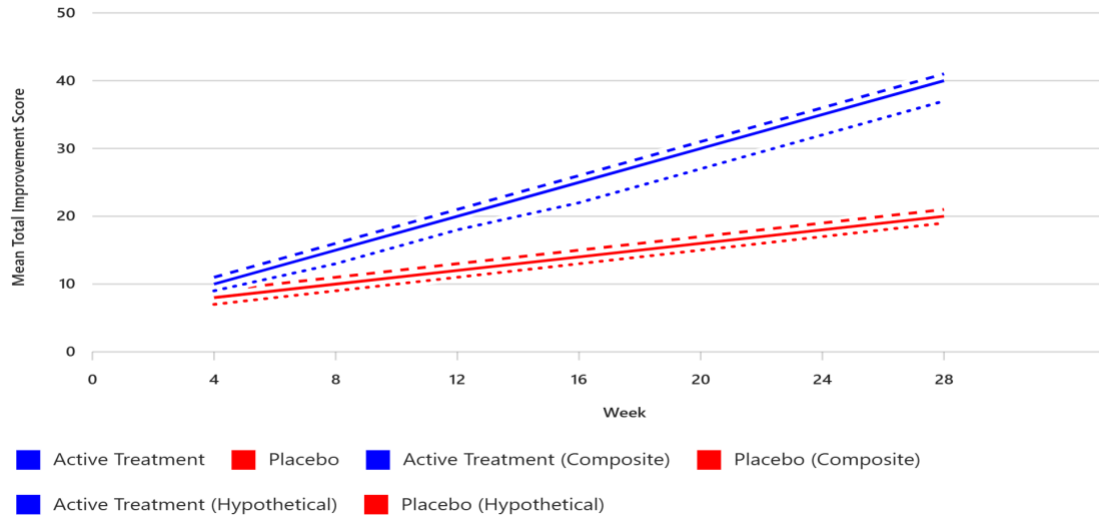

FIGURE 3: Primary Estimand: ANCOVA: Line plot of TIS Least-Squares Mean (Full Analysis Set) .

The mock figure can be interpreted as: plot for Hypothetical - Models outcome as if no intercurrent events occurred.

Composite - Includes intercurrent events as part of the endpoint and Treatment Policy - Uses all observed data regardless of events. (Basically ignored.)

TABLE 6:

Table 1: Tabulation of Intercurrent Events (Full Analysis Set)

Analysis Window/ Intercurrent Event	Active (N=18)	Placebo (N=22)	All Subjects (N=40)
Week 8			
Any Intercurrent Event	0	1 (4.5)	1 (2.5)
Composite variable intercurrent events			
Any composite variable intercurrent events	0	1 (4.5)	1 (2.5)
Early permanent treatment discontinuation due to lack of efficacy from Week 4 onwards up to and including Week 28	0	1 (4.5)	1 (2.5)
Required Rescue Medication Week 4 onwards up to and including Week 28	0	0	0
Confirmed deterioration from Week 4 onwards up to and including Week 28	0	0	0
Hypothetical strategy	0	0	0
Early permanent treatment discontinuation before Week 4 or for any reason other than lack of efficacy	0	0	0
..... Repeated till Week 28.....			

All intercurrent events occurring in the study are contained in this table. If a subject has more than one intercurrent event, the first in time will be used for analysis. Subjects may be counted in more than one category, but will be counted only once within a category. Intercurrent events are presented for all analysis windows after the intercurrent event occurs.

The mock table can be interpreted as: All the intercurrent events captured in the ADICE are described here by analysis timepoints and details on each ICE strategy captured in dataset affecting the number of subjects at various timepoints.

TABLE 7:

Listing 1: Listing of Intercurrent Events (Full Analysis Set)

Treatment Group/ Subject ID	Date of First IP Intake	Medication/Discontinuation Reason	Intercurrent Event	Date (Day [1])
ACTIVE				
ABC001001	02APR2025	ADVERSE EVENT	Hypothetical Strategy: Early permanent treatment discontinuation before Week 4 or for any reason other than lack of efficacy	30APR2025 (29)
ABC001002	06SEP2024	METHYLPREDNISONE	Composite Strategy: Intake of rescue medication from Week 4 onwards p to and including Week 28	27NOV2024 (83)

The mock listing can be interpreted as: The similar content of the dataset ADICE would be detailed in the listing.

ADAM IMPLEMENTATION ON DATA COLLECTION

(as per example case study)

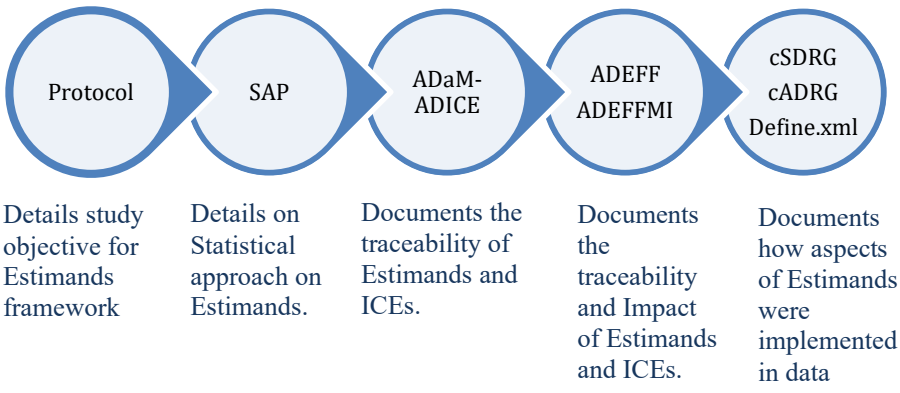

FIGURE 4: Diagram explaining Data collection for Estimand implementation in ADaM.

DIAGRAM FOR ADAM IMPLEMENTATION ON DATA ANALYSIS.
(as per example case study)

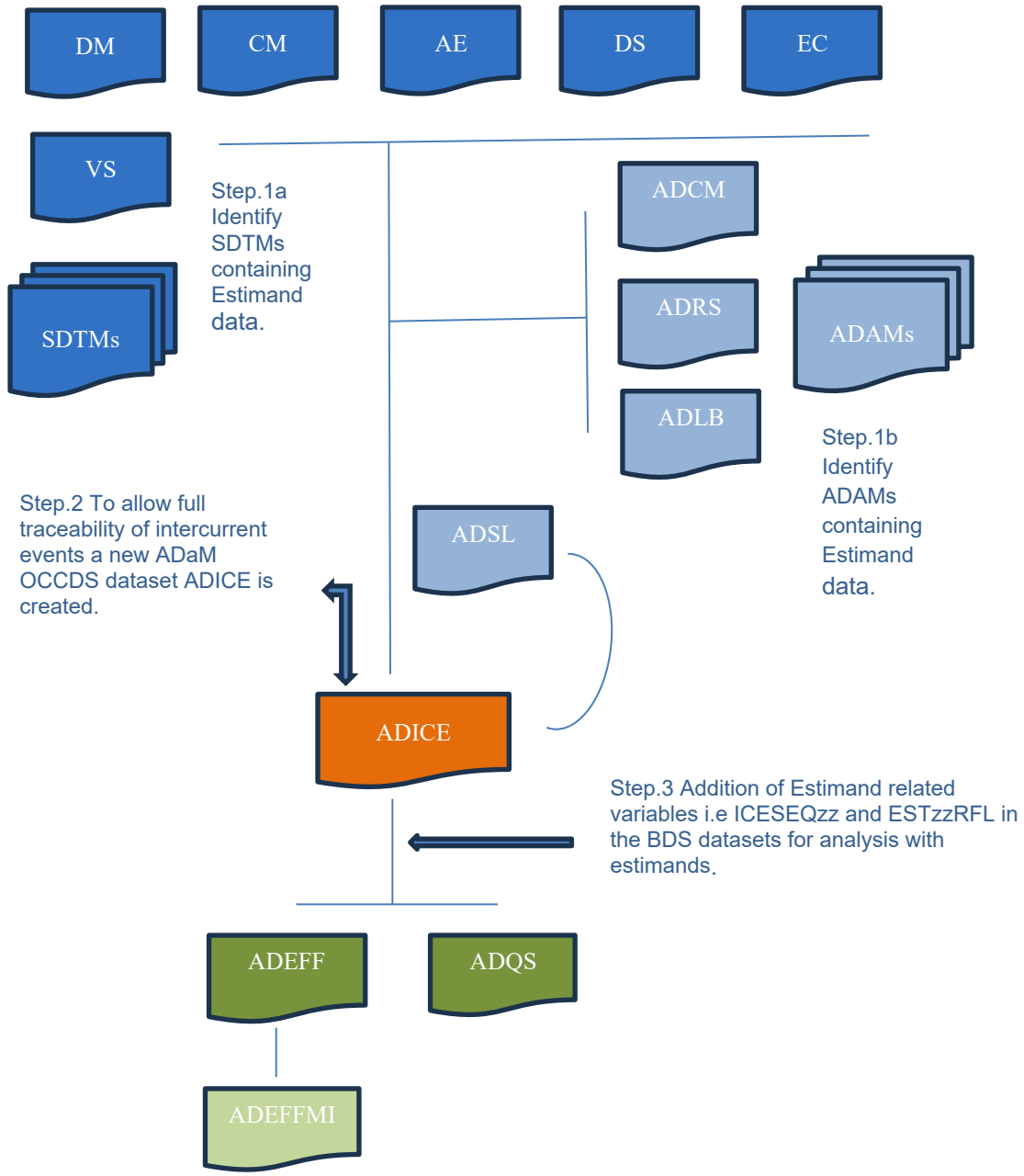

FIGURE 5: Diagram explaining Data Analysis for Estimand implementation in ADaM.

CONCLUSION

- The 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 correctly, 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 basic guidance on how estimands in a study could be implemented in ADaM datasets and how different strategies for intercurrent events can be handled with a few outputs showing effects of ICE. Using this straight-forward approach, programmers and the review of clinical studies can benefit from a clear structure.
- One of the important learning I had during the implementation of estimand 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 intimidating

as it can be based on many different SDTM and ADAM sources, it will help to invest enough effort to construct this dataset properly for Analysis outputs accuracy.
- ADICE would become base for the estimand analysis and influence changes in other datasets containing variables of interest, it is therefore as important as the analysis itself. From my experience working on this dataset - a clear structure and thoughtful planning of implementation is of utmost importance for 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

[3] Estimands implementation using data standards https://www.cdisc.org/sites/default/files/2024-04/2024_CDISC-Session%207B%20ADaM_DAVISTER%20COCHINAIRE_Estimands.pdf

ACKNOWLEDGMENTS

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RECOMMENDED READING

[1] ICH E9(R1) Estimands and Sensitivity Analysis in Clinical Trials - Training Module 1: Summary. Updated Dec 2021.

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