

What is an Estimand?

- An **Estimand** is a precise description of the treatment effect that a clinical trial aims to estimate. It ensures that the **trial objectives**, **data collection**, and **statistical analysis** are aligned.

According to ICH E9(R1), an estimand has **five key attributes**:

Attribute	Description
Treatment	The intervention(s) being compared
Population	The group of patients targeted for inference
Variable	The outcome or endpoint being measured
Intercurrent Events	Events occurring after treatment initiation that affect interpretation
Summary Measure	The statistical method used to quantify the treatment effect

What are Intercurrent Events?

- **Intercurrent events (ICEs)** are events that occur **after treatment starts** and can: **Prevent** the observation of the outcome, **Change** the interpretation of the outcome, **Impact** the relevance of the treatment effect.



What are the different strategies of handling ICEs for the clinical trial?

Composite variable Strategies	• The ICE is considered as a part of the outcome and is incorporated into the definition of the endpoint • e.g., Early permanent treatment discontinuation due to lack of efficacy, Rescue medication usage..
Hypothetical Strategies	• Treatment Effects are estimated in the hypothetical situation where the relevant ICE would not have taken place. • e.g., Early permanent treatment discontinuation for any reason other than lack of efficacy
Treatment Policy Strategies	• ICEs are deemed to be irrelevant when estimating the treatment effect of interest. • e.g., 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. • 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 occurrence of the ICE is of interest. • e.g., the last measurement before death(or other ICEs) or at a predefined timepoint, whichever comes first.

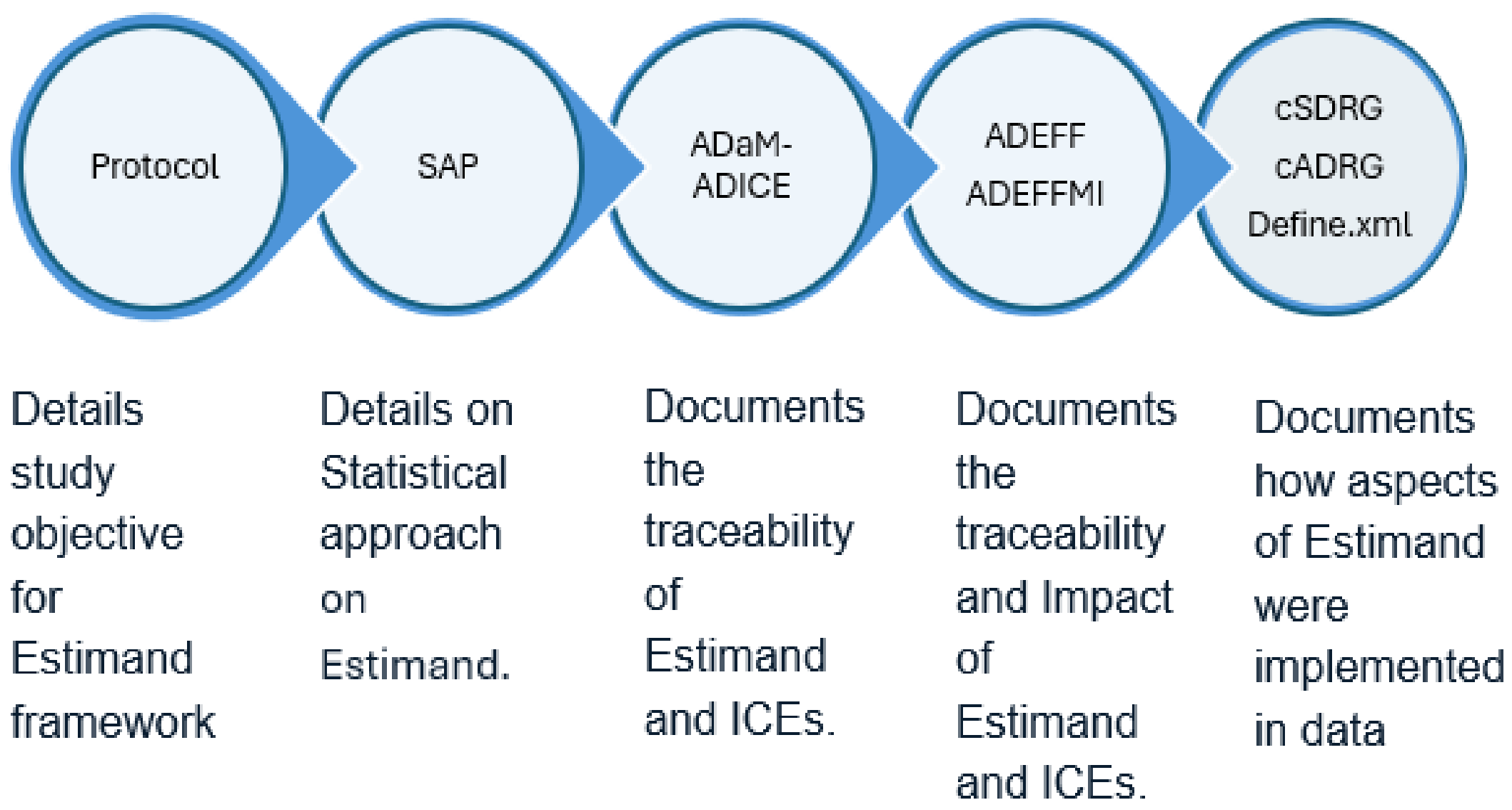
Conclusion:

- **To Handle the different Strategies of ICEs, follow the recommended guidance^[2] to create analysis dataset ADICE with Occurrence Data Structure (OCCDS) facilitating traceability and supporting harmonized workflow.**
- **Additional variables such as ICESEQzz, ESTzzRFL and ICEzzFL should be added to applicable ADaM datasets. These are crucial in ensuring the analysis outcome is correct.**
- **A thorough understanding of the identified ICEs and their handling strategies is essential for accurately translating the Estimand analysis from the SAP to the study results**

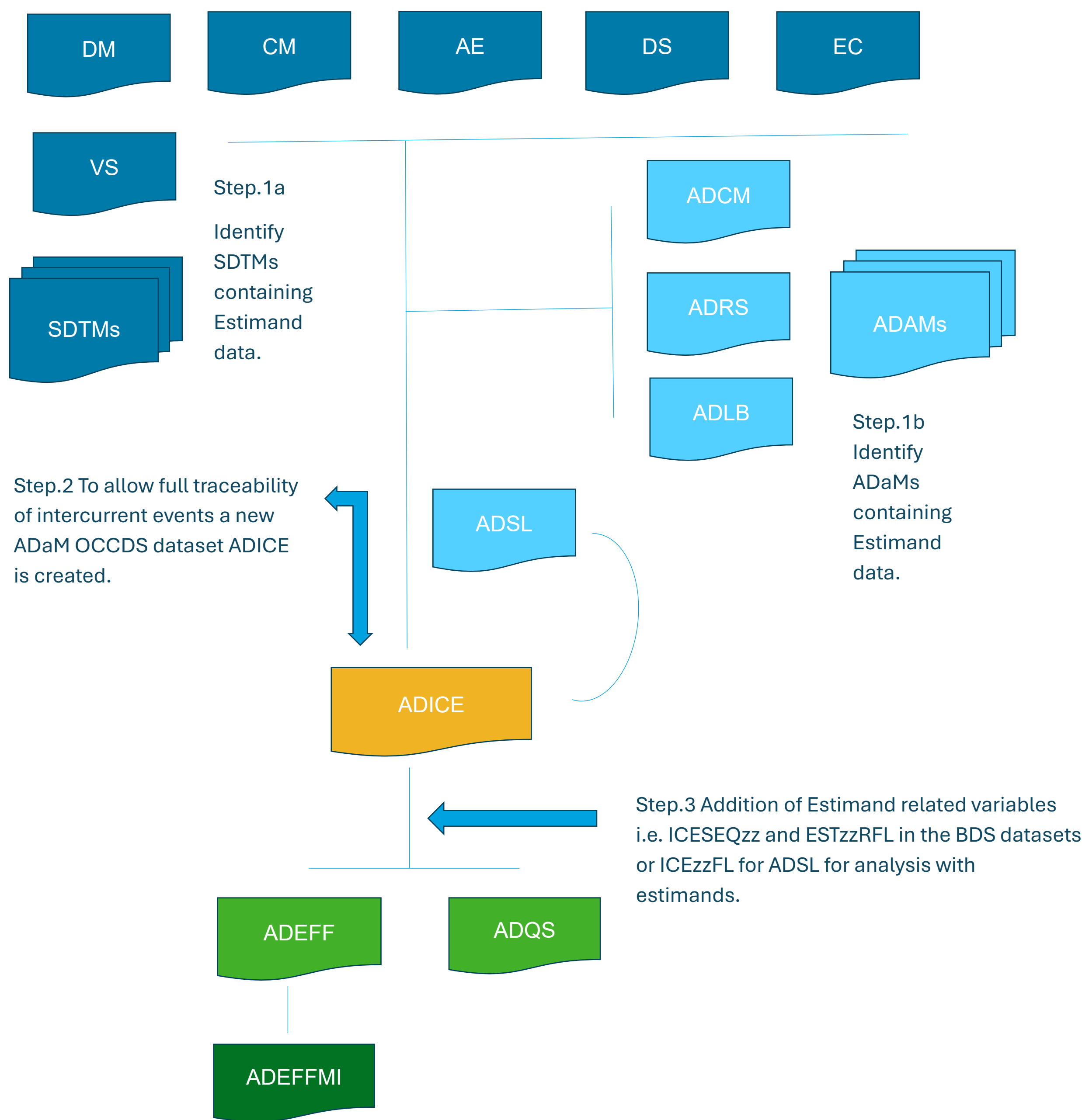
ADaM Implementation for ICE – ADICE

(as per example case study)

➤ Data Collection & Documentation:



➤ ADaM creation and consequences:



How to approach ICE Implementation:

- A clear understanding of the Estimand section in the SAP is the essential first step toward progressing to subsequent phases.
- The second step is to identify and accurately map sources detailing intercurrent events - a task that can be complex when definitions span multiple datasets such as SDTMs, ADaMs.
- The third step is to develop ADICE and determine which ADaM datasets are impacted by ICE, ensuring they are updated accordingly for analysis.
- Finally, select observations carefully for Estimand related analysis Outputs.
- Estimand implementation can be tricky and intimidating to understand if you are programming such a dataset for the first time.

[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 Harmonization 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>