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# Programming Perspective: Streamline Estimands, Strategies, and Design ADaM for Estimands

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## ABSTRACT

Estimands, which define the treatment effect to be estimated, introduced by ICH E9 (R1) in November 2019, and it has been incorporated into an increasing number of clinical trials, and has become a key concept in clinical trial design. The ICH E9 (R1) mentioned the concept of estimand, and important considerations related to the clinical trial planning, design, conduct, analysis etc, but no specific implementation instructions for programmers. To help programmer easily implement estimands in clinical trials, it's essential to break down the concept into clear, manageable components and relate them to practical programming tasks. Estimands components, intercurrent events handling strategies, corresponding general data handling are introduced and summarized. Specifically, it is designed to demonstrate a flexible ADaM structure that is compatible with various strategies. It can record multiple intercurrent events separately and supports different types of analyses, like main analysis, sensitivity analysis, and supplementary analysis. A dummy case study is illustrated for programmer to implement estimands with ease: understand the estimands framework, grasp the definition of study intercurrent events and handling strategies, build up ADaM to capture intercurrent events information, construct efficacy ADaMs, conduct analysis.

## INTRODUCTION

The ICH E9 (R1) estimand concept is not mandatory in all clinical trials, but it is highly recommended and increasingly adopted to improve the clarity and relevance of clinical trial results. Regulatory agencies, such as the FDA, EMEA and NMPA, encourage its use to ensure that trial objectives and outcomes are well-defined and meaningful. Adoption of the estimand framework can enhance the quality and interpretability of trial data, making it a valuable tool for clinical research. The concept of the estimand can be used widely among different scenarios, like different across therapeutic areas (oncology, cardiovascular disease, neurology, infectious diseases etc.), different types of trials (equivalence trials, non-inferiority trials, complex innovative trials, multi-regional clinical trials, considerations of real-world data, etc), different trial objectives (safety, early phase clinical trials, vaccine clinical trials, etc.), and the handling of some special concomitant events (treatment switching, COVID-19 pandemic-related events, etc.).

An estimand is a precise description of the treatment effect reflecting the clinical question posed by a given clinical trial objective. Estimand concept generally is pre-specified in protocol, then effectively captured during CRF design and study conduct. More details about estimand may be specified in Statistical Analysis Plan (SAP), like estimand attributes, intercurrent events and corresponding data handling strategies, and its implementation in kinds of analyses like sensitivity analysis, supplementary analysis etc. In this paper, choice of strategies, and the priority of strategy for handing multiple intercurrent events are not discussed.

For programmers, based on the SAP and Table Figure Listing (TFL) Shell definitions, it is essential first to understand Intercurrent Events (ICE) defined in the project and corresponding strategies for addressing ICEs. Specially, if multiple intercurrent events occur for the same patient, check SAP to understand which strategy is considered as priority. Secondarily, it is crucial to understand the differences among the strategies and potential impact on the datapoints that need analyses. Thirdly, once these concepts are clear, construct the ADaM datasets, integrate ICE in ADaM according to the analysis requirements. Finally, apply the processed data points in the specific TFL analyses.

## ESTIMANDS

The ICH E9 (R1) stated that intercurrent events are events occurring after treatment initiation that affect either the interpretation or existence of the measurements associated with the clinical question of interest. It is necessary to address intercurrent events when describing the clinical question of interest in order to

precisely define the treatment effect that is to be estimated. Here are some examples about intercurrent events:

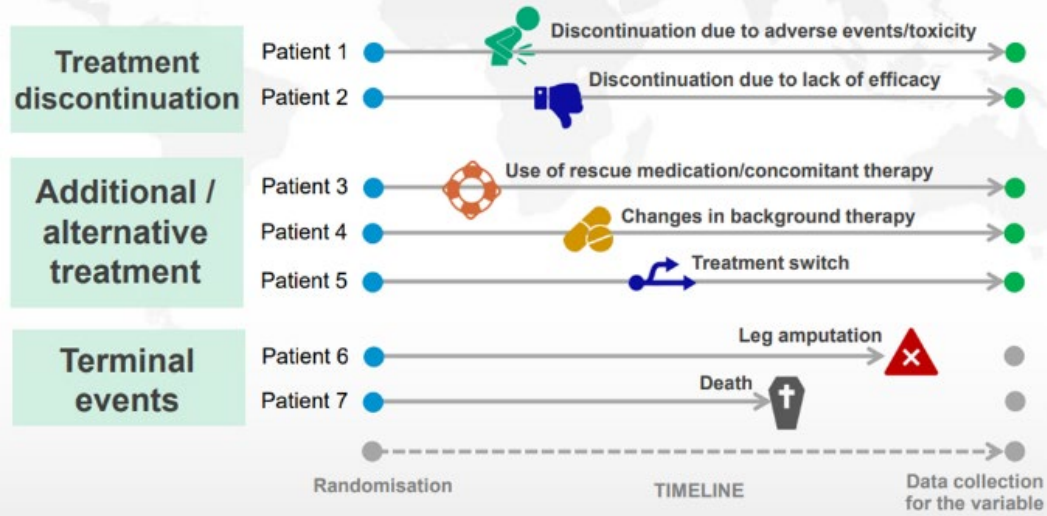


**Figure 1. Common Intercurrent Events**

Strategies for addressing intercurrent events in clinical trials are essential to maintain the integrity of the estimands, ensure accurate estimation of treatment effects, enhance the validity of trial results, comply with regulatory requirements, facilitate meaningful interpretation, and support informed decision-making. The ICH E9 (R1) stated five possible strategies to address intercurrent events. From programmer's perspectives, they can be broken down as examples below:

- Treatment policy strategy:
    - all observed values of relevant variable are used, regardless of whether or not ICE occurs.
- Hypothetical strategies:
    - assuming the intercurrent event does not occur. Values observed after the occurrence of ICE are NOT included in analysis.
    - Variable value collected after ICE may need to be imputed/predicted before analysis.
- Composite variable strategies:
    - ICE considered to be informative about a patient's outcome and is therefore incorporated into the endpoint definition.
    - Not limited to dichotomous endpoints.
    - For example, if a patient takes rescue medication it may be considered that the allocated treatment was not effective, and the patient was not successfully treated. If the outcome is already success/failure, use of rescue would dictate treatment failure.
- While on treatment strategies:
    - response to treatment prior to the occurrence of the ICE is of interest.
    - This strategy can impact on the definition of the endpoint.
    - For example, the last measurement before death (or other ICE) or at a pre-defined timepoint, whichever comes first.
    - Compared with 'Hypothetical strategies', the main difference is using this strategy, the variable value collected after ICE were not included in analysis, and NO need to be

imputed/predicted neither as analysis endpoint definition generally up to the occurrence of ICE.

- Principal stratum strategies:
    - relate to the population who are potentially not going to experience ICE (or those who will experience ICE).

Besides, to better understand for programmers, I summarized some common data handling examples using programming logic for each strategy as below Table 1:

- ASTDT: observed values assess date.
- ICEDT: intercurrent event occur date.
- AVAL/AVALC: observed values of assessment.

| **Strategies** | **Data Handling Examples** |
|---|---|
| Treatment policy strategy | Ignore ICE, no action |
| Hypothetical strategies | If ASTDT > ICEDT, then AVAL/AVALC is disregard, and need to be imputed/predicted based on SAP. |
| Composite variable strategies | Case1: If ASTDT > ICEDT, then AVALC = non-responder regardless of whether it satisfies the responder derivation criteria.<br>Case2: If ASTDT > ICEDT, then AVAL = worst observation carried forward.<br>Case3: If ASTDT > ICEDT, then AVAL = baseline observation carried forward.<br>Case4: If ASTDT > ICEDT, then AVAL = trimmed means. |
| While on treatment strategies | To address the clinical question more accurately, when adopt this strategy, it affects the definition of endpoint. And if ASTDT > ICEDT, then AVAL/AVALC = null. AVAL/AVALC **not** need to be imputed/predicted before analysis. |
| Principal stratum strategies | Mark subject whether or not experience ICE in subject level. No special data handling in record level about AVAL/AVALC. |

**Table 1. Common Data Handling Examples Corresponding to Estimand Strategies**

The strategies mentioned before can be used alone or combination to address different intercurrent events. And if SAP mentioned any missing data imputation method for analysis, not included in estimand strategy, applied estimand strategy, then do the data processing.

To implement this concept in analysis, the ICH E9 (R1) also mentioned five attributes about estimand, including treatment, population, variable (or endpoint), intercurrent event and population-level summary. From programmer's perspectives, they can be broken down as below understanding and examples:

- Treatment:
    - Treatment condition of interest, and treatment to be compared.
    - Examples:
        - A new biologic therapy administrated vs. subcutaneous injection every two weeks.
- Population:
    - Patients targeted by the clinical question.
    - Examples:

        - Adults aged 18-75 with moderate to severe asthma who are not adequately controlled with standard inhaled corticosteroids.

- Variable (or endpoint):
    - the specific outcome or variable that is being measured.
    - Examples:
        - binary response/non-response at week 12.
        - change from baseline in PASI at week 52.
        - time from randomization to progression disease.
- Intercurrent events:
    - Precise specifications of treatment, population and variable are likely to address many of the intercurrent events considered in sponsor and regulator discussions of the clinical question of interest. Any other intercurrent event that have not yet addressed in the specification of treatment, population or variable, specified here.
    - Examples:
        - Discontinued study intervention due to COVID-19.
- Population-level summary:
    - Provides a basis for comparison between treatment conditions.
    - Examples:
        - For a binary variable/endpoint – proportions or difference of proportions.
        - For a normal distribution endpoint – means or differences of means.
        - For a time-to-event endpoint – hazard ratio or t-year event-rate difference.

## CONSTRUCT ADAM

The estimand framework is described in the protocol and SAP, therefore impacting most of the related statistical analyses. Such a broad 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:

- Incurrent Events: provides ways to organize, identify, and document intercurrent events, their relationship with each estimand and the related handling strategy.
- Analysis Datapoints: provides ways to document analysis datapoints affected by intercurrent events.

After we understand the basic terminologies about estimands, programmer then might consider how we design in ADaM to meet analysis requirements. These datasets can be divided into 2 groups:

- ADICE: datasets gathering the intercurrent events
- Other ADaM datasets: datasets supporting the statistical analyses related to estimands

The ADICE dataset is built at the very beginning of the analysis data to serve as support for documenting the impact of intercurrent events into the other ADaM datasets supporting the statistical analyses. With the creation of ADICE, it's easy to identify datapoints affected by intercurrent events and to trace back to those intercurrent events affecting them. To support that purpose, intercurrent events should ideally be organized and consolidated in a structure facilitating the identification and documentation. More details can be referred to below steps.

### Step 1. ADICE

First, suggest creating an individual Occurrence Data Structure (OCCDS) structure ADaM – ADICE. The source of ADICE could be SDTM or ADaM. The ADICE can record each occurred intercurrent events, the occur date of each intercurrent event, the intercurrent event category etc. Proposing an individual ADICE in ADaM for dealing with ICE provides a structured, transparent, and consistent approach to managing intercurrent events. This simplifies the tracking and management of ICE, making it easier to apply consistent handling strategies across different analyses, facilitates the implementation of different handling strategies (i.e., hypothetical strategies). The structure and key variables of ADICE would be listed in below Table 2:

| Variables | Core | Notes |
|---|---|---|
| USUBJID | Req | Unique subject identifier |
| ASEQ | Perm | Unique number per record, per subject, per intercurrent event. |
| SCRDOM | Perm | Name of the parent dataset holding the intercurrent event. Normally the name of the parent SDTM domain. It could also be another ADaM dataset. Include if SRCSEQ is included. |
| SRCSEQ | Perm | Sequence number of the intercurrent event record in parent domain. |
| ASTDT | Perm | Source start date of the intercurrent event in numerical format. |
| ICETERM | Perm | Specific term describing the intercurrent event. |
| ICECAT | Perm | Category of intercurrent event (e.g., discontinuation, rescue medication use) |
| AOCCFL | Perm | Record the 1st occurrence of intercurrent event within subject. |
| ESTzzSTR | Perm | Strategy for handling the intercurrent events related to estimand zz.<br>Subject level strategy used only when each subject implemented only one strategy for one estimand even though it has multiple intercurrent events.<br>Note: If multiple intercurrent events occur and potentially affect a datapoint from a timing perspective, refer to SAP to identify the one to consider in priority, and mark the strategy used for this estimand in this variable. |

**Table 2. Key Variables of ADICE**

## Step 2. Basic Data Structure (BDS) ADaM

Then, since all subjects that who experienced ICE already been captured in ADICE, we can integrate key information from ADICE with other ADaM datasets (e.g., ADPASI) through USUBJID variable to apply the data handling strategies. The key information in ADICE depends on the data handling strategies, generally could be subject level intercurrent event strategy etc. With the ICE information, we can derive new analysis parameters per different strategies different estimands (e.g., main estimand, supplementary estimand). Examples might be below:

| Variables | Core | Notes |
|---|---|---|
| USUBJID | Req | Unique subject identifier |
| PARAM | Req | The description of the analysis parameter.<br>Can derive new parameters that handled by intercurrent events strategies per analysis need. For example, original PARAM is ‘AAA’, new PARAM handled by ICE strategies for estimand 01 could be ‘AAA Estimand 01’. |
| AVISIT | Perm | Analysis visit. |
| ADT | Cond | Analysis date. |
| AVAL | Cond | Analysis value |
| ESTzzSTR | Perm | Copy from ADICE, keeps it as subject level estimand zz handling strategy. |

| Variables | Core | Notes |
|---|---|---|
| CRIT1 | Perm | A text string indicates that record value changed per estimand zz handling strategy. |
| CRIT1FL | Cond | Character flag indicating the criterion defined in CRIT1 is met on the record. |

**Table 3. Key Variables of BDS ADaM**

## CASE STUDY

As limited cases about 'While on treatment strategies' and 'Principal stratum strategies', this paper only present data handling cases for other three common strategies. The construct about ADaM is similar across different strategies.

This is a randomized, double-blind, placebo-controlled, multicenter protocol to evaluate the safety and efficacy of Drug A in subjects with moderately to severely active Crohn's Disease. The primary endpoint is change from baseline in the CDAI score at week 12.

The primary estimand (estimand 1) components are listed in below Table 4 and Table 5. This is a dummy case study, the choice of strategy is not discussed in this paper.

| | |
|---|---|
| **Treatment** | Drug A vs. Placebo 200 mg SC at Week 0, 4, and 8 |
| **Population** | Subjects 18 years or older with moderately to severely active Crohn's disease. |
| **Variable (or endpoint)** | Change from baseline in the CDAI score at Week 12 |
| **Population-level Summary** | Difference in means of change from baseline between treatment group Drug A and the placebo. |

**Table 4. Estimand Attributes in Case Study**

| ICE Categories No. | ICE Categories | Strategies | Data Processing Rules |
|---|---|---|---|
| 1 | Chron's disease-related surgery | Composite variable strategies | CDAI data after ICE are replaced by the baseline score for CDAI |
| 2 | Prohibited medication list changed in Crohn's disease medication | Composite variable strategies | CDAI data after ICE are replaced by the baseline score for CDAI |
| 3 | Discontinuation of study intervention<br>• Due to lack of efficacy or an AE of worsening Crohn's disease | Composite variable strategies | CDAI data after ICE are replaced by the baseline score for CDAI |
| 4 | Discontinuation of study intervention<br>• Due to COVID-19 | Hypothetical strategy | CDAI data at all visits after an ICE are set to missing (statistical methods can handle the missing data) |

| ICE Categories No. | ICE Categories | Strategies | Data Processing Rules |
|---|---|---|---|
| 5 | Discontinuation of study intervention<br>• Due to other reasons | Treatment policy strategy | All observed values of the variable will be used |

Note: In this case, when multiple ICEs occur on same subject, the overall strategy is based on the first ICE.

**Table 5. Intercurrent Events and Strategies in Case Study**

The ADaM build up steps are below:

## Step 2. ADICE

In ADICE dataset, all intercurrent events are captured in it.

- **ICETERM**: Each specific ICE is collected here for traceability and documentation.
- **ICECAT(N)**: The ICE category (number) is collected here for further strategy chosen.
- **AOCCFL**: The first occurred ICE of a subject is marked as "Y".
- **EST01STR**: The overall strategy of estimand 1 of a subject is populated here.

**Row 1**: Subject ABC001 has one ICE, ICE category number is 5 (ICECATN=5), per Table 5, corresponding strategy for this estimand 1 is treatment policy strategy (EST01STR=" Treatment policy strategy").

**Rows 2-3**: Subject ABC002 has two ICEs (ICECATN=2, ICECATN=3), and per note in Table 5, overall strategy is based on earliest occurred ICE (ASTDT=16AUG2021), thus AOCCFL is marked as 'Y' on row 2, the overall strategy for this subject (both row 2 and row 3) is composite variable strategies (EST01STR="Composite variable strategies").

**Row 4**: Subject ABC003 has one ICE, ICE category number is 1 (ICECATN=1), per Table 5, corresponding strategy for this estimand 1 is composite variable strategies (EST01STR="Composite variable strategies").

**Row 5**: Subject ABC004 has one ICE, ICE category number is 4 (ICECATN=4), per Table 5, corresponding strategy for this estimand 1 is hypothetical strategy (EST01STR="Hypothetical strategy").

| Row | USUBJID | ASEQ | SRCDOM | SRCSEQ | ASTDT | ICETERM | ICECAT | ICECATN | AOCCFL | EST01STR |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | ABC001 | 1 | DS | 7 | 26JUL2021 | Withdrawal by subject | Subjects who discontinued study intervention due to other reasons | 5 | Y | Treatment policy strategy |
| 2 | ABC002 | 1 | FA | 2 | 16AUG2021 | Initiated a protocol-prohibited medication X | Prohibited medication list changed in Crohn's disease medication | 2 | Y | Composite variable strategies |
| 3 | ABC002 | 2 | DS | 9 | 13SEP2021 | AE – worsen of Crohn's disease | Subjects who discontinued study agent due to lack of efficacy or due to an AE of worsening of Crohn's disease | 3 | | Composite variable strategies |
| 4 | ABC003 | 1 | PR | 2 | 12AUG2023 | Colectomy | Subjects who had a Crohn's disease-related surgery | 1 | Y | Composite variable strategies |
| 5 | ABC004 | 1 | AE | 1 | 24AUG2022 | COVID-19 | Discontinuation of study intervention due to COVID-19 | 4 | Y | Hypothetical strategy |

**Table 6. Structures and Contents of ADICE in Case Study**

## Step 2. BDS ADaM

With ADICE, the core information can be integrated or merged into the original analysis dataset model, which already includes analysis datapoints (parameters) that do not implement the estimand concept. This allows for the creation of new parameters incorporating the estimand to handle updates to the datapoints effectively.

- **FICECATN**: The earliest intercurrent event category number, derived from ADICE (populate as ADICE.ICECATN when ADICE.AOCCFL="Y").
- **FICEDT**: The earliest intercurrent event occur date, derived from ADICE (populate as ADICE.ASTDT when ADICE.AOCCFL="Y").
- **EST01STR:** The strategy to address ICE of this subject, derived from ADICE (populate as ADICE.EST01STR when ADICE.AOCCFL="Y").
- **CRIT1FL:** Populated as 'Y' when corresponding analysis value (AVAL) changed per estimand 01 strategy.
- **Rows 1-6:** Subject ABC001, per ADICE, this subject experienced intercurrent event category 5, the corresponding strategy is 'Treatment policy strategy', it means no special data handling needed. Thus, for new created PARAM 'CDAI Total Score Estimand 01', the AVAL directly copy AVAL from PARAM 'CDAI Total Score'.
- **Rows 7-16:** Subject ABC002, although this subject experienced multiple intercurrent events category 2 and 3, but per multiple intercurrent events handling rule in this example, select the earliest intercurrent event date to confirm strategy. Thus, for this subject, the earliest intercurrent event occur date is 16AUG2021, any assessment date after this occur date would use corresponding strategy 'Composite variable strategies'. Thus, for new created PARAM 'CDAI Total Score Estimand 01' that occurred after earliest intercurrent event date, the AVAL is set as baseline CDAI total score. Refer to row 16, at week 12, we changed AVAL from original '200' to baseline '400', and mark CRIT1FL as 'Y' to display it's changed value considered estimand strategy.
- **Rows 17-26:** Subject ABC004, per ADICE, this subject experienced intercurrent event category 4, the corresponding strategy is 'Hypothetical strategy', it means any assessment date after earliest occur event date (24AUG2022) is set to null. Thus, refer to row 26, at week 12, we changed AVAL from original '250' to null, and mark CRIT1FL as 'Y' to display it's changed value considered estimand strategy.

| Row | USUBJID | PARAM | AVISIT | ADT | AVAL | FICECATN | FICEDT | EST01STR | CRIT1 | CRIT1FL |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | ABC001 | CDAI Total Score | Baseline | 11JUN2021 | 200 | 5 | 26JUL2021 | Treatment policy strategy | | |
| 2 | ABC001 | CDAI Total Score | Week 4 | 09JUL2021 | 300 | 5 | 26JUL2021 | Treatment policy strategy | | |
| 3 | ABC001 | CDAI Total Score | Week 8 | 06AUG2021 | 250 | 5 | 26JUL2021 | Treatment policy strategy | | |
| 4 | ABC001 | CDAI Total Score Estimand 01 | Baseline | 11JUN2021 | 200 | 5 | 26JUL2021 | Treatment policy strategy | AVAL changed per estimand 01 strategy | |
| 5 | ABC001 | CDAI Total Score Estimand 01 | Week 4 | 09JUL2021 | 300 | 5 | 26JUL2021 | Treatment policy strategy | AVAL changed per estimand 01 strategy | |
| 6 | ABC001 | CDAI Total Score Estimand 01 | Week 8 | 06AUG2021 | 250 | 5 | 26JUL2021 | Treatment policy strategy | AVAL changed per estimand 01 strategy | |

| Row | USUBJID | PARAM | AVISIT | ADT | AVAL | FICECATN | FICEDT | EST01STR | CRIT1 | CRIT1FL |
|---|---|---|---|---|---|---|---|---|---|---|
| 7 | ABC002 | CDAI Total Score | Baseline | 21JUN2021 | 400 | 2 | 16AUG2021 | Composite variable strategies | | |
| 8 | ABC002 | CDAI Total Score | Week 4 | 17JUL2021 | 500 | 2 | 16AUG2021 | Composite variable strategies | | |
| 9 | ABC002 | CDAI Total Score | Week 6 | 31JUL2021 | 550 | 2 | 16AUG2021 | Composite variable strategies | | |
| 10 | ABC002 | CDAI Total Score | Week 8 | 14AUG2021 | 500 | 2 | 16AUG2021 | Composite variable strategies | | |
| 11 | ABC002 | CDAI Total Score | Week 12 | 25SEP2021 | 200 | 2 | 16AUG2021 | Composite variable strategies | | |
| 12 | ABC002 | CDAI Total Score Estimand 01 | Baseline | 21JUN2021 | 400 | 2 | 16AUG2021 | Composite variable strategies | AVAL changed per estimand 01 strategy | |
| 13 | ABC002 | CDAI Total Score Estimand 01 | Week 4 | 17JUL2021 | 500 | 2 | 16AUG2021 | Composite variable strategies | AVAL changed per estimand 01 strategy | |
| 14 | ABC002 | CDAI Total Score Estimand 01 | Week 6 | 31JUL2021 | 550 | 2 | 16AUG2021 | Composite variable strategies | AVAL changed per estimand 01 strategy | |
| 15 | ABC002 | CDAI Total Score Estimand 01 | Week 8 | 14AUG2021 | 500 | 2 | 16AUG2021 | Composite variable strategies | AVAL changed per estimand 01 strategy | |
| 16 | ABC002 | CDAI Total Score Estimand 01 | Week 12 | 25SEP2021 | 400 | 2 | 16AUG2021 | Composite variable strategies | AVAL changed per estimand 01 strategy | Y |
| 17 | ABC004 | CDAI Total Score | Baseline | 04JUN2022 | 350 | 4 | 24AUG2022 | Hypothetical strategy | | |
| 18 | ABC004 | CDAI Total Score | Week 4 | 02JUL2022 | 250 | 4 | 24AUG2022 | Hypothetical strategy | | |
| 19 | ABC004 | CDAI Total Score | Week 6 | 15JUL2022 | 200 | 4 | 24AUG2022 | Hypothetical strategy | | |
| 20 | ABC004 | CDAI Total Score | Week 8 | 29JUL2022 | 150 | 4 | 24AUG2022 | Hypothetical strategy | | |
| 21 | ABC004 | CDAI Total Score | Week 12 | 26AUG2022 | 250 | 4 | 24AUG2022 | Hypothetical strategy | | |
| 22 | ABC004 | CDAI Total Score Estimand 01 | Baseline | 04JUN2022 | 350 | 4 | 24AUG2022 | Hypothetical strategy | AVAL changed per estimand 01 strategy | |
| 23 | ABC004 | CDAI Total Score Estimand 01 | Week 4 | 02JUL2022 | 250 | 4 | 24AUG2022 | Hypothetical strategy | AVAL changed per estimand 01 strategy | |
| 24 | ABC004 | CDAI Total Score Estimand 01 | Week 6 | 15JUL2022 | 200 | 4 | 24AUG2022 | Hypothetical strategy | AVAL changed per estimand 01 strategy | |
| 25 | ABC004 | CDAI Total Score Estimand 01 | Week 8 | 29JUL2022 | 150 | 4 | 24AUG2022 | Hypothetical strategy | AVAL changed per estimand 01 strategy | |
| 26 | ABC004 | CDAI Total Score Estimand 01 | Week 12 | 26AUG2022 | NULL | 4 | 24AUG2022 | Hypothetical strategy | AVAL changed per estimand 01 strategy | Y |

**Table 7. Structures and Contents of ADICE in Case Study**

After all data handled by estimand strategies, all statistical analysis or missing data handling can be conducted as normal. In another words, the corresponding parameters can be selected to do missing data imputation if needed per SAP, and then the parameters can be used in table statistics calculation.

## CONCLUSION

In conclusion, for programmer, there are some keys to integrate estimands in study:

1. Understand intercurrent events, specially ensure precise data mapping to categorize intercurrent events.
2. Gain a deep understanding of each data handling strategy, specially one subject might have multiple intercurrent events occurrence. Be attentive to priority of data handling strategies, and whether the strategies are utilized alone or combination.
3. Recognize there are primary (main) estimands, as well as supplementary estimands etc. in the study, each estimand may have different data handling strategy.
4. Different ADaM implementation approaches are appropriate to satisfy analysis requirements.

This paper has underscored the critical importance of integrating estimand strategies, and efficient ADaM design within programming frameworks. By streamlining these elements, programmer can enhance the precision and reliability of clinical trials data analysis. This holistic approach not only strengthens the foundation of evidence-based medicine but also advances the collective goal of improving patient outcomes through rigorous and transparent data analysis practices.

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